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CERTAIN MODERN AGENTS FOR THE DETECTION AND ABOLITION OF SUSCEPTIBILITY TO DIPHTHERIA.[1]

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SECTION I.

Introduction.

THE prophylactic agent which we in Australia know as anatoxin consists of diphtheritic toxin produced by the growth of diphtheritic bacilli in veal broth and rendered non-toxic by treatment with formaldehyde. The name "anatoxin" is of French origin, being given to the product fourteen years ago by Ramon, of the Pasteur Institute. English and American workers have preferred to call the product "toxoid", and in English-speaking countries that name is now generally accepted. In the British Pharmacopœia of 1932 the words "toxoid" and "anatoxin" are regarded as synonymous.

For a number of years past efforts have been made to increase the immunizing effect of this product. Various substances have been added to it with the object of decreasing the rate of its absorption. Thereby one hoped to prolong the immunizing stimulus and so to increase the immunizing effect. Of these substances, the one which has been most widely used is alum, that is, potassium aluminium sulphate ($KAlSO_4$, $12H_2O$).

Certain American authorities some years ago simply added a very small quantity of alum to

[1] Read at the fifth session of the Australasian Medical Congress (British Medical Association), August, 1937.

toxoid and used the resultant mixture, without refinement, for the immunization of human beings. This procedure never passed the experimental stage and need not be further considered. Instead, we may discuss the product known as "diphtheria toxoid (alum-precipitated)", or sometimes known as "alum-toxoid" or as "alum-precipitated toxoid", or simply as "a.p.t." This is the product of which one dose is said to confer immunity upon the great majority of recipients. The administration of this one dose is known as the "one-shot" method.

When in 1931 and 1932 alum-precipitated toxoid was first introduced, hopes were held that it would supersede ordinary toxoid. Some of the earlier reports were particularly sanguine. Since then many trials of this product have been made. We are now in a better position to decide whether alum-precipitated toxoid has a place in the prophylaxis of diphtheria in Australia. We may compare ordinary toxoid with alum-precipitated toxoid. No prophylactic agent other than these two need at present be regarded as being of the same order of general usefulness.

Diphtheria toxoid (alum-precipitated) is, in its simplest and most primitive form, prepared as follows:

> To a quantity of toxoid alum is added. A copious white precipitate is thrown out and allowed to settle to the bottom. The supernatant fluid is removed and discarded. The precipitate is washed twice with normal saline solution and resuspended in fresh normal saline solution. This suspension constitutes the final product.

Made in this way the product was used by Graham, Murphree and Gill,[2] by Walker[4] and by others, who first tested it on human beings. Since then refinements in the method of production have been introduced and alum-precipitated toxoid has been widely used. In the following sections are tabulated and analysed a number of papers in which its use is reported. In the original papers the brands of alum-precipitated toxoid which were used are sometimes mentioned, sometimes not. No single brand has proved outstanding either on account of its immunizing or on account of its irritant properties.

SECTION II.

Abstracts of Published Reports upon Diphtheria Toxoid (Alum-Precipitated).

Abstracts of published reports on diphtheria toxoid (alum-precipitated) are set out in Tables I, II and III.

SECTION III.

A Review of the Articles to Which Reference is Made in Section II.

The Immunizing Power of the Product.

The evidence regarding the efficacy of one dose of alum-precipitated toxoid is conflicting. If one accepts as the criterion of success the immunization, as judged by the Schick test, of approximately 90% of the total recipients, then an analysis of the reports yields the following. On eight occasions, concerning in all 6,886 children, one dose of alum-precipitated toxoid succeeded. On another eight occasions, concerning in all 3,218 children, one dose of alum-precipitated toxoid failed.

Among those authors who reported failures, one must make special mention of Bousfield,[12][23] because he has had much experience of prophylactic agents and because his report is one of the most recent of those available. Bousfield is the medical officer in charge of immunization against diphtheria in Lambeth, Camberwell, Fulham and other suburbs of London. In 1936 he tested two brands of alum-precipitated toxoid, giving one dose of one or the other to a number of children, who at that time were all Schick-positive. Three months later the children were subjected to the Schick test. Of those who had been treated with one brand of alum-precipitated toxoid, 80% no longer reacted to the Schick test; of the others, 37% only failed to react. Bousfield concludes that if one-shot alum-precipitated toxoid

> . . . as at present constituted, is the only method practicable in rural areas, the whole thing were better left alone unless parents are warned that there will be many failures, or unless confirmatory Schick testing can be provided with a reasonable certainty that children who have received only one injection will be brought for this test in due course.

Those are Bousfield's own words. He stated that the area in which his work was conducted was a semi-rural one within twenty miles of Charing Cross. As a rule it is more difficult to immunize a rural community than an urban one.

The evidence indicates that as a rule two doses yield very good results. On separate occasions Chesney,[17] Parish,[18] Powell,[22] and Bousfield[23] found two small doses very effective. On the other hand, McSweeney,[5] working with two doses of 1·0 cubic centimetre, was less fortunate. He immunized only 77·3% of the recipients.

The Duration of the Immunity Conferred.

Doubt has been cast upon the duration of the effect of alum-precipitated toxoid. Volk[11] found a tendency to revert to the Schick-positive condition among children who were apparently successfully immunized. Walker[4] also noted that phenomenon. Pansing and Schaffer[26] reported that a group of 549 children were given 1·0 cubic centimetre of alum-precipitated toxoid and were subsequently found not to react to the Schick test. Two years later they were retested. Only 42·2% were found to be still non-reactors to the Schick test. On the other hand, Farago,[15] making a direct test on no less than 2,379 children in order to elucidate this point, found no evidence of any such reversion over a period of ten months.

The finding that one dose of alum-precipitated toxoid confers a less durable immunity than do three doses of ordinary toxoid is borne out by work performed by Fraser at the Connaught Laboratories, Toronto, Canada. Fraser (N. E. McKinnon and Mary A. Ross[19]) compared the content of antitoxin produced in the blood of human beings by one dose of alum-precipitated toxoid with that pro-

duced by three doses of ordinary toxoid. The estimations were made in each instance ten weeks after the commencement of immunization. Of patients who had been given one dose of alum-precipitated toxoid, 62% had attained a titre of more than one one-hundredth of a unit per cubic centimetre of blood. Of those who had had three doses of toxoid, 91% had attained that titre.

The estimations were repeated twelve months after the commencement of immunization. Of the

TABLE I.

Abstracts of Reports which Indicate the Degree of Immunity Conferred.

Author.	Reference Number.	Date of Experiments Reported.	Circumstances of each Campaign.	Number of Recipients of a.p.t.	Proportion of Recipients Successfully Immunized.
Saunders	1	1931	Four widely differing batches of a.p.t. used. To some of the recipients three doses were given.	436, most of whom were not previously Schick tested.	60% to 100% according to batch and number of doses.
Graham, Murphree and Gill.	2	1933	Single dose of a.p.t. given.	185, all previously "Schick-positive".	92·4%.
				613, not previously Schick tested.	96·6%.
A. A. Walker ..	4	1933	One dose of 1 c.c. of a.p.t. given.	300, all previously "Schick positive".	100%.
				1,789, not previously Schick tested.	100%; all 2,089 were tested from two to six months after the dose.
C. J. McSweeney ..	5	1934	Direct comparison of a.p.t. and anatoxin (formol-toxoid). Both were supplied by the same laboratory. 2 c.cs. of each product constituted a course. Anatoxin was given in two doses; a.p.t. was given in two, three, or four doses. All children originally "Schick positive". Re-tested four weeks after the last dose (rather early for good results).	58.	Anatoxin successfully immunized 88·1%, and was definitely more successful than a.p.t., which immunized 77·3%.
Keller and Leathers ..	6	1934	One dose of 1 c.c. of a.p.t. given.	76, all previously "Schick positive".	98·7%, nearly all within twenty-eight days of the dose.
E. A. Underwood ..	7	1934	One dose of 1 c.c. of a.p.t. given.	152, all previously "Schick positive".	83·6%, tested one month after the dose.
J. E. Haine	8	1935	One dose of 0·5 c.c. of a.p.t. to some. One dose of 1 c.c. of a.p.t. to others.	794, none being previously "Schick tested".	91·2%.
Naughten, White and Foley.	9	1935	One dose of 1 c.c. of a.p.t.	130, all previously "Schick positive".	93·0%.
The Editor, *The Journal of the American Medical Association.*	10	1935	A large campaign conducted in Washington County. One dose of a.p.t.	1,446, all previously "Schick positive".	79·8% (tested from three to seven months after the dose).
V. K. Volk	11	1935	One dose of a.p.t. The natural immunity of the community was low.	304.	65% to 70%.
W. G. Patterson ..	14	1935	One dose of 1 c.c. of a.p.t. to some. One dose of 0·5 c.c. of a.p.t. to others.	57 children, all previously "Schick positive".	89·5%.
F. Farago	15	1934	One dose of 1 c.c. of a.p.t. given.	2,652, all previously "Schick positive".	93·5%.
M. Isabolinski *et alii* ..	16	1935	One dose of 1 c.c. of a.p.t. given.	150, all previously "Schick positive".	96·8%.
G. Chesney	17	1935	Two doses of a.p.t. given, the first of 0·1 or 0·2 c.c., the second of 0·4 c.c.	162, all previously "Schick positive".	99·38%.
H. J. Parish	18	1935	One dose of 0·5 c.c. or of 1 c.c. of a.p.t. given.	352.	65·5%.
			Two doses of a.p.t. given, the first of 0·1 c.c., the second of 0·2 c.c. or 0·5 c.c.	164.	99·3%.
L. Kositza	20	1934–35	Six different brands of a.p.t. tried. One dose given, either of 0·5 c.c. or 1 c.c.	335.	86·3%. No brand or brands were outstandingly effective.
A. Powell	22	1935–36	In 1935, one dose of 0·5 c.c. a.p.t.	197.	100%.
			In 1936, one dose of 0·5 c.c. a.p.t.	297.	81·4%.
			In 1936, a group received two doses, 0·1 c.c. followed in fourteen days by 0·4 c.c.	100.	99%.
G. Bousfield	23 (See also 12)	1936	One dose of 1 c.c. of a.p.t.	100, all previously "Schick positive".	37%, when tested three months after the dose.
			One dose of 0·5 c.c. of a different brand.	175, all previously "Schick positive".	80%.

NOTE.—The abbreviation a.p.t. refers to diphtheria toxoid (alum-precipitated).

TABLE II.

Abstracts of Reports which Indicate the Duration of the Immunity Conferred.

Author.	Reference Number.	Date of Experiments Reported.	Circumstances of each Campaign.	Evidence Indicating the Duration of the Immunity.
A. A. Walker	4	1933	One dose of 1 c.c. of a.p.t. given.	Forty children re-tested two years after having been successfully immunized. One had reverted to the "Schick positive" condition.
V. K. Volk	11	1935	One dose of a.p.t. given.	One hundred and seventy children who were "Schick negative" from four to six weeks after the dose were re-tested six months later. Sixteen (9·4%) had reverted to the "Schick positive" condition.
F. Farago	15, 21	1933–1936	One dose of 1 c.c. of a.p.t. given.	Two thousand three hundred and seventy-nine children were tested two months and, again, twelve months, after receiving the dose. There was no evidence of loss of immunity during the intervening ten months.

NOTE.—The abbreviation a.p.t. refers to diphtheria toxoid (alum-precipitated).

first group, only 19% still had a titre of one one-hundredth of a unit; of the second group, 91% still had that amount. Fraser admitted that the numbers of persons in the groups were small, respectively 40 and 35. He interpreted his observations as indicating that one dose of alum-precipitated toxoid was inferior to three doses of unmodified toxoid.

The Irritant Effect of the Product.

A similar conflict of opinion is noted. In eight of the articles quoted[2][4][6][9][10][13][15][16] the authors were apparently satisfied that the reactions, as observed, were neither sufficiently numerous nor sufficiently intense to constitute a contraindication to the method. Nevertheless, in four of these

TABLE III.

Abstracts of Reports which Indicate the Intensity of the Irritant Effect of the Product.

Author.	Reference Number.	Date of Experiments Reported.	Evidence Regarding the Reactions Produced.
Saunders	1	1931	Author states that "when administered in properly graduated doses the reactions caused by alum-toxoid are not more severe than those caused by toxoid-antitoxin".
Graham, Murphree and Gill	2	1933	Seven hundred and ninety-eight children each given one dose of a.p.t. No mention of reactions.
Saunders	3	1933	Continuation of work referred to under reference (1), above. This time there were very severe reactions, including four instances of abscess at the site of injection and two of induration, lasting many months. As the batches of material employed were experimental, no stress need be laid on this report.
Walker	4	1933	Two thousand and eighty-nine children, up to twelve years of age, were each given one dose of 1 c.c. of a.p.t. No mention of reactions except that, of 135 infants, aged six to eighteen months, none had a reaction other than an occasional slight induration.
Kellers and Leathers	6	1934	Out of seventy-six children, six developed temperatures of more than 37·8° C. (100° F.) The highest was 38·6° C. (101·4° F.). They required rest in bed. Local reactions occurred in these children, but there were no abscesses. The authors were not alarmed by these reactions.
Undgrwood	7	1934	One hundred and sixty-three children, all "Maloney negative", received one dose of 1 c.c. of a.p.t. Two children suffered a severe local reaction, a diffuse, brawny hardening of the arm soon subsiding. Nine children, all "Maloney positive", received one dose of 0·3 c.c. of a.p.t. Six of them suffered severe local and general reactions. The author states that the Maloney test should not be omitted.
Haine	8	1935	One thousand one hundred children given one dose each of a.p.t. In those under ten years of age, there occurred moderate reactions only, relatively few in number. In those over ten there occurred some severe reactions. Seventeen adults were given one dose; two of them suffered severe local and general reactions. The author states that he will not again use a.p.t. for persons over twelve years of age. To another hundred persons he gave two doses each of 0·1 c.c. of a.p.t. at an interval of seven days. The severity and the number of the reactions were so noticeably more than by the single-dose method that the double-dose method was abandoned.
Naughten, White and Foley	9	1935	One hundred and thirty children received one dose of 1 c.c. of a.p.t. Nearly all suffered some reaction. In six there were brawy induration with hyperæmia over the whole arm, stiffness in the joints and local heat, taking six days to subside In one a small sterile abscess developed. The authors do not consider that reactions of this severity need constitute a contraindication of the use of the method.
The Editor, *Journal of the American Medical Association.*	W 10	1935	Among five thousand one hundred children, each receiving one dose of a.p.t., severe reactions were rare. Two children developed urticaria and œdema, which disappeared within twenty-four hours.
Bousfield	12 (see also 23)	1934	He is opposed to any existing one-dose method except for institutions where the children are all young and under medical supervision. He considers that the number and severity of the reactions produced by a.p.t. are likely to bring discredit upon artificial immunization.
Waterfield	13	1934	The author disagrees with Bousfield. He injected fifty children, between the ages of six and thirteen years, with a.p.t. He found that in only six did slight, local reactions follow. He found that adults certainly suffered more reaction, some constitutional signs and local tenderness.
Patterson	14	1935	The author supports Bousfield. He gave twenty-three schoolgirls 1 c.c. each of a.p.t. Twenty of them showed definite local reactions, red, very tender, indurated areas of from one to three inches in diameter, rising to their height on the third day. He also gave twenty children in a residential institution each 1 c.c. of a.p.t. Their ages were six to fifteen years. The local reactions were sufficiently severe to make him chary of using the preparation outside residential institutions.
Farago	15	1934	He observed sixty thousand inoculations of a.p.t. He apparently used no Maloney test nor substitute therefor. He states that the reactions caused by a.p.t. are of the same frequency and intensity as those caused by ordinary toxoid. He observed in a small percentage of instances (0·01% to 0·3%) cold abscesses which healed spontaneously. (It must be noted that the author accepts as immaterial after both ordinary toxoid and after a.p.t. reactions which we should regard as severe, namely, high fever—101·3° F.—in 0·7% of those inoculated, vomiting in 0·23%, constant local pain in 2% and hyperæmia, extending over half the upper arm in 1%.)
Isabolinski	16	—	Two hundred and forty-five children each received one dose of 1 c.c. of a.p.t. Thirty-four (14%) suffered moderately severe general and local reactions, including an increase of temperature to from 38·4° C. to 39·5° C. (101° F. to 103° F.), headache, nausea and, in five cases, diarrhœa. Locally there appeared severe redness and swelling. No abscesses occurred; but in several cases there developed induration which was not completely absorbed for seven days. The authors did not consider these reactions dangerous, as they all subsided after a short time.
Chesney	17	1935	Two small doses of a.p.t. (0·1 c.c. and 0·4 c.c.) were used. The first dose was used as a "detector" dose, to detect sensitivity to toxoid. In spite of this precaution moderate local reaction occurred after the second dose in 8% of one hundred and eighty children.
Parish	18	1935	Two small doses of a.p.t. (0·1 c.c. and 0·2 c.c.) were used. Thirteen of the recipients had given weak positive reactions to the Maloney test. A "few mild or moderate" reactions resulted. One child had a moderately severe local reaction which persisted for several days after each injection.
Kositza	20	1934–1935	Six different brands of modern a.p.t. were employed. Among seven hundred and seventy-six recipients there occurred eight abscesses which required incision, six which healed without incision, and twenty-nine instances of softening of the tissues which did not advance to abscess formation. No brand of a.p.t. was outstanding. The author stated that "the relative frequency of abscess formation in children over five years of age makes it questionable whether the product can be accepted as the sole immunizing agent at present".

NOTE.—The abbreviation a.p.t. refers to diphtheria toxoid (alum-precipitated).

eight,[6][9][15][16] reactions are described that were definitely more severe than is desirable, and apparently more severe than would be tolerated in Australia.

Moreover, in five others of the articles quoted,[7][8][12][14][20] the authors were frankly alarmed and did not intend to use alum-precipitated toxoid again without some safeguard, such as the Maloney test or the selection of recipients according to age.

Among those who were dissatisfied one must make special mention of Kositza,[20] because she tested six different brands of modern alum-precipitated toxoid. She and her collaborators administered one dose to each of 776 recipients. She observed eight abscesses which required incision, six which healed without incision, and twenty-nine instances of softening of the tissues which did not advance to abscess formation. No brand of alum-precipitated toxoid was without this irritant tendency. The author stated that "the relative frequency of abscess formation in children over five years of age makes it questionable whether the product can be accepted as the sole immunizing agent at present".

The administration of alum-precipitated toxoid in two small doses was found innocuous by Parish,[18] but not by Haine,[8] who reported severe reactions following two doses each of 0·1 cubic centimetre. Chesney,[24] using two small doses, as recently as April, 1937, found that sterile abscesses still occasionally occurred.

SECTION IV.

Comments upon the Results Reported in Sections II and III.

There is conflict of opinion on the significance of the results reported in Sections II and III. There is no general agreement regarding the efficacy of the product and none regarding its irritant properties. This may be at least partially explained. One explanation is that the name "diphtheria toxoid (alum-precipitated)" and its synonyms have been applied to a product which has from time to time been profoundly modified. Though regarded by the general body of medical practitioners as a clearly defined and well-established biological preparation, it is in reality not so. It invariably consists of diphtheritic toxoid precipitated by alum and resuspended in saline solution. That is true. But an infinite variety of modifications of that formula is possible. The composition of the original toxoid may vary; so may the amount of alum added; so may the treatment of the toxoid before the addition of the alum, or of the precipitate after the addition of the alum.

Made as it was originally, according to the simple procedure outlined above, alum-precipitated toxoid is a powerful immunizing agent. That is admitted, apparently universally. It is, however, irritant. It causes local and general reactions, and occasionally sterile abscesses. Attempts have been made to modify the product to eliminate the irritant effect. In consequence various laboratories have each produced their own brand. There is evidence not only that the product of one laboratory differs from that of another, but also that individual laboratories have from time to time made changes in the method of preparation of their own product.

No British or international regulations have as yet been laid down in order to control the issue of alum-precipitated toxoid. The Therapeutic Substances Regulations of Great Britain, of 1935, lay down certain tests to which any diphtheria prophylactic must conform. These tests are devised to control ordinary toxoid, toxoid-antitoxin floccules, and others of the older prophylactic agents. They are intended merely to ensure that the specific toxicity of the toxin used has been adequately reduced and that potency as an immunizing agent has been retained. These tests are not specially devised, nor are they suitable for the control of alum-precipitated toxoid. On the other hand, American regulations have been laid down in order to control the issue of alum-precipitated toxoid. The National Institute of Health has devised special regulations for this purpose. For instance, the finished product must not contain more than 20·0 milligrammes of alum per human dose. No such regulation, however, can ensure that the product shall be entirely non-irritant to human beings.

In a leading article in *The British Medical Journal* of October 10, 1936,[27] a statement is made that the health authorities of New York City have decided recently to cease the issue of alum-precipitated toxoid.

SECTION V.

What Attitude Should We in Australia Adopt Towards Diphtheria Toxoid (Alum-Precipitated)?

Most brands of alum-precipitated toxoid are potent immunizing agents. Nevertheless, they are not so exceedingly potent that one dose is adequate for the immunization of almost all of the recipients. If reliance is placed upon one dose, a large proportion of the recipients will remain susceptible and those upon whom immunity is conferred may lose that immunity before long. The "one-shot" method is liable to cause a false sense of security and to bring discredit upon our efforts.

Is a "two-shot" method practicable? Those of us who work constantly with prophylactic agents realize the effect of a multiplicity of injections. A second stimulus is of greatly increased effect by virtue of the very fact that a first stimulus has gone before it. The first stimulus increases the reactivity of the recipient. Two well-spaced doses of alum-precipitated toxoid should confer an immunity as firm and as durable as do three doses of ordinary toxoid. This is borne out by our own experiments upon animals and by the reports of those who have used two doses overseas. But there is evidence that two doses, although each is small, may cause objectionable reactions.

At the Commonwealth Serum Laboratories we have set ourselves to prepare an alum-precipitated toxoid which shall be innocuous, that is, one which

will cause no abscesses whatever and reactions only of a mild and local character. We have endeavoured by our investigations to ascertain whether such a product will be effective in two doses, even more effective than are three doses of ordinary toxoid. If such a product could be prepared and could be administered without any preliminary test of the sensitivity of the recipients, that is, without a preliminary Maloney test, an advance would have been made. I may remark in passing that Saunders[25] was unable to avoid reactions following the administration of alum-precipitated toxoid by selecting recipients according to the Maloney test. Certain severe reactions occurred in persons who did not react to the Maloney test.

We have prepared a number of experimental batches of alum-precipitated toxoid, one of which has been tested not only upon laboratory animals, but also on human beings. Two small doses were given, namely, 0·25 and 0·5 cubic centimetre. No objectionable reactions have resulted. It is as yet too soon to report on the immunizing effect. Experiments upon animals indicate that this product is, volume for volume, more potent than is ordinary toxoid.

In conclusion, I may mention certain of the other agents which have been recommended for the prophylaxis of diphtheria. Toxin-antitoxin mixture is now practically obsolete. It is not as satisfactory as is ordinary toxoid. When each is given in the doses advised, the toxoid has the greater immunizing power.

Toxin-antitoxin floccules and toxoid-antitoxin floccules, though not of recent introduction, have, for various reasons, never gained widespread acceptance. Their general usefulness is not equal to that of toxoid.

Jensen, of the State Serum Institute, Copenhagen, has recently reported preliminary experiments with toxoid precipitated by aluminium hydroxide, $Al(OH)_3$, instead of alum. He administers one subcutaneous dose of this product and follows it by intranasal instillation of purified toxoid. This procedure must as yet be regarded as experimental. We have used aluminium hydroxide as a precipitating agent for toxoid, but do not as yet desire to report upon it.

Summary.

1. The most suitable prophylactic agent both for large-scale campaigns and for the immunization of individuals or small groups is ordinary toxoid (anatoxin).

2. Diphtheria toxoid (alum-precipitated), if administered in one dose only, may leave a large proportion of the recipients still susceptible to the disease. Moreover, it may occasionally cause severe local and general reactions, even small sterile abscesses.

3. Insufficient evidence has as yet been accumulated to determine whether diphtheria toxoid (alum-precipitated) administered in two doses is fully effective and whether it is innocuous.

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DIPHTHERIA IMMUNIZATION.[1]

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SINCE diphtheria prophylaxis was commenced in South Australia some years ago over 16,000 children have received treatment, about 11,000 being in country districts.

[1] Read at the fifth session of the Australasian Medical Congress (British Medical Association), August, 1937.

In the city active immunization has met with a mixed reception. Fortunately I have had undivided and enthusiastic support in my own district of Hindmarsh, where we followed up our last year's campaign in February.

Number of Patients Treated at Hindmarsh.

One hundred and ninety-seven children applied for treatment when the request forms were sent out, without preliminary advertisement. Shortly afterwards the anti-vivisectionists sent to the members of my municipal council a sheet of extracts, some of which I found impossible to verify as to their consistency either with the context or with fact. The local board was unaffected; but the distribution of the circulars to individual school children resulted in thirty-seven withdrawals. One hundred and sixty attended for treatment in the first instance, but there were a further twenty-three withdrawals after this, still apparently due to the depredations of the enemy. There were fourteen reactions to anatoxin such as I described in my previous paper.[1] Seven positive Maloney reactions were found. These twenty-one children were Schick-tested and none reacted; in one case there was a definite pseudo-reaction. This pseudo-reactor had reacted to anatoxin with the thirteen others of the first group, none of whom reacted to the Maloney test.

About 40% of those treated belonged to the age group five to seven years inclusive; but eleven of the reactors to anatoxin were children over this age. In a group of twenty-six medical students whose average age was about twenty years, eleven were Schick positive, and seven others who may have had pseudo-reactions were regarded as Schick positive also. Ten students were Maloney tested, five reacting; two of these reactions were severe and were accompanied by axillary adenitis. Eleven Schick-positive students received injections of anatoxin, including the five Maloney-positive reactors, who, it will be remembered, were Schick-positive. Nine out of eleven reacted to anatoxin after the first, second or third dose. Doses of 0·01 cubic centimetre were given to the positive Maloney group; one of these became quite sore at the site of injection and suffered from general adenitis with the first injection.

One, whose Maloney response was not so great as in the case just quoted, was given 0·1 cubic centimetre as a commencing dose and had no reaction. Fourteen days later he was given 0·5 cubic centimetre and sustained a general reaction with loss of sleep and malaise and pronounced extensive reddening of the skin; there was no adenitis.

All received two injections, and those permitted to proceed with the prophylaxis received three injections at intervals of three weeks and two weeks respectively. Eleven were Schick tested ten weeks after the last injection and ten did not react. The man who reacted was the only one who did not react to anatoxin at the site of inoculation; but he developed an urticaria. Tron, of Milan, observed thirty-four patients with a second attack of diphtheria, fifteen of whom had suffered from serum sickness during the primary attack and twenty-one in the second attack.[2] The Schick conversion in the reactors to anatoxin mentioned above is confirmation of the tentative conclusion reached in my report last year, that it is probably unnecessary to continue the administration of anatoxin to those subjects who, being non-reactors to the Maloney test, react to prophylactic doses of anatoxin.

The Schick Test.

On August 8, at Largs Bay, there were initiated 71 Schick tests with controls and Maloney tests. Eleven of the subjects were adults, the remainder being sixteen years of age and under. The Maloney tests were read 24 and 48 hours later. The Schick tests were read 72 and 96 hours after inoculation. The controls were read with the Maloney tests and were practically undetectable by the fourth day except in one or two instances. The readings showed 39 and 17 Maloney and pseudo-reactions respectively at the end of 24 hours. At the end of 48 hours the readings were 33 and 12 reactions respectively. There were three delayed Maloney reactions. This shows that the reactions are not due to mere trauma, but to some substances present in the inocula, and it is unsafe to rely on readings for the Maloney reaction taken only on the second day; also that despite the assertions made by some people the Schick pseudo-reaction is not the same as and cannot replace the Maloney reaction.

Efforts have been made for some time to find a stable diluent for diphtheritic toxin for Schick testing. Recently Adey and Paterson[3] have described the production of a Schick fluid diluted ready for use issued by the Commonwealth Serum Laboratories. This material was used for the first time in South Australia in these tests. It is difficult to say how great a boon this preparation is in circumstances in which, owing to the inadequacy of the equipment or the total lack of such in the non-existent health services of this State, one has to improvise on the spot or provide from one's own pocket. This remark does not apply to the administrative part played by the Central Board of Health, which has always given the utmost assistance. Not only is the preparation handy, but the batch used has many other advantages, which are well set out by Merrillees.[4] The particularly uniform clarity of the readings and the absence of doubtful reactions in comparison with experiences over some years with the previous preparations, made the reading a pleasure instead of necessitating a consultation over every fifth or sixth arm.

I do not agree with Merrillees, however, on the uniformity of size of the positive Schick reaction; eleven of the thirty-six areas of reaction had a diameter greater than 2·5 centimetres (one inch), being approximately 3·0 centimetres in diameter. My numbers are small; but actually the pronounced remission in intensity spoken of on the fourth day was represented by a greater intensity on this day in nine individuals out of the thirty-six; but on four occasions the reaction was greater on the fifth day. The remainder were the same on each occasion.

On the third day there were thirty-four Schick-positive reactions, and on the fourth, thirty-six. (These days correspond to Merrillees's fourth and fifth days.) Three patients transferred to the Northfield Infectious Diseases Hospital reacted also. Two of these had a delayed Maloney reaction on the fifth and sixth days. Some children gave strongly positive Maloney reactions with Schick pseudo-reactions of varying extent and definitely positive Schick reactions. Numerous children gave strongly positive Schick reactions without a pseudo-reaction or a positive Maloney reaction. It was quite common to find a positive Maloney reaction without a pseudo-reaction or a Schick reaction, that is, with Schick immunity. In two instances a positive control was found without an accompanying positive Maloney reaction. Of twelve children who had been transferred to the Northfield Infectious Diseases Hospital carrying morphological *Corynebacterium diphtheriæ* four were Schick positive five to six weeks afterwards.

The accompanying table, supplied by Dr. Finger, Superintendent of the Northfield Infectious Diseases Hospital, shows the clinical condition of these children. It would appear that E.K., who reacted strongly to the Schick test forty-five days after her illness began, suffered a clinical attack of diphtheria; and yet this period should have been ample time to develop sufficient antibody to neutralize the Schick toxin, unless there was complete absence of primary stimulus when the infection first appeared and the 16,000 units of antitoxin prevented its origin, or she was one of those patients who are spoken of as "very resistant". These remarks apply in a lesser degree to the other three Schick-positive reactors in the table.

E.K. did not react at all to the Maloney test or to a control injection. An injection of 0·5 cubic centimetre of anatoxin was given on August 15. The next day there was an area of reaction 2·5 centimetres (one inch) in diameter. On August 17 it had enlarged to 3·75 by 5·0 centimetres (one and a half inches by two inches) and was a dull brown in colour. It had not been painful.

D.S., aged twelve years, who reacted weakly to the Schick test and had moderately severe faucial and nasal diphtheria and received 30,000 units of antitoxin, reacted strongly to the Maloney test and control injection. An area of reaction 2·5 centimetres (one inch) in diameter appeared twenty-four hours after the injection of 0·1 cubic centimetre of anatoxin; but in forty-eight hours the area was diffusely red and tender.

All four patients, including E.K. and D.S., were "Schick-negative" on December 5, 1937, after three injections of anatoxin.

As these reactions fade a certain amount of purplish pigmentation is left; this is also true of the stronger Maloney reactions. The pigmentation is more widespread in many instances than the Schick pigmentation ever is, although the colour is approximately the same.

It is obvious when these tests are done together that the substance responsible for the Maloney reaction is different from that which causes the Schick control response. That each of these is different again from the positive Schick reaction is obvious also. The anatoxin may represent a deamination or even a detoxicating polimerization of the toxin molecules.[5] Since deamination is always accompanied by decarboxylization, may not the formation of formic acid be responsible for the beesting-like pain felt after the injection of anatoxin?

The immunization schemes conducted in the metropolitan area have been subject to some fallacies and in many instances the apparent failure has been due to these. Many children do not get the full course of anatoxin, some receiving one dose only instead of three, and there has been a tendency to give the doses at too short intervals. The average interval has been about three weeks, in some cases two weeks, and in one instance of which I have heard a week's interval was all that was allowed. One cannot help feeling that this last arrangement was the result of misplaced enthusiasm. These schemes do not allow the full antigenic response to develop, since the antitoxin concentration reaches its maximum from ten to thirty days after an injection of anatoxin. It would seem from this that five weeks may be a better spacing.[6]

Frequently one has observed that the manner of inoculation can be at fault unless due care is exercised. The material may leak back past the plunger of the syringe. The injection may be given intramuscularly, or the anatoxin may leak out through the puncture in the skin.

So far there has been no follow-up with routine Schick testing; consequently no adequate idea of the Schick conversion rate can be made.[1] A 95% conversion rate may be expected in an already

[1] This has been done at Largs Bay where approximately a 94% conversion rate was obtained on December 5.

TABLE I.

The Clinical Condition et cetera of Children Admitted to the Northfield Infectious Diseases Hospital.

Patient.	Age.	Result of Schick Test.	Duration of Illness in Days Before Admission.	Amount of Antitoxin. (Units.)	Date of Admission.	Remarks.
J.Q.	10	−	1	16,000	June 22, 1937.	Moderate faucial lesion; tonsils grossly diseased.
P.H.	9	+	?	10,000	June 25, 1937.	Mild faucial lesion; tonsils grossly diseased.
K.T.	11	+	?	4,000	July 1, 1937.	Contact; no virulence test done.
E.K.	7	+	1	16,000	June 29, 1937.	Moderate faucial lesion; carditis on twelfth day, lasting fourteen days.
D.S.	12	+	1	30,000	June 25, 1937.	Moderate faucial and nasal lesion; tonsils grossly diseased; definite acute antritis.
V.O'C.	11	−	1	20,000	June 24, 1937.	Moderate faucial lesion; tonsils grossly diseased.
L.R.	15	−	—	4,000	August 4, 1937.	Admitted as suspect; no evdience of diphtheria infection found.
B.C.	13	−	—	4,000	August 4, 1937.	Admitted as suspect; no evidence of diphtheria infection found.
V.O'B.	10	−	—	8,000	June 25, 1937.	Contact; positive swab once only; discharged July 4, 1937.
P.K.	10	−	?	6,000	June 29, 1937.	Very mild faucial lesion; positive swab once only.
G.B.	9	−	??	8,000	July 1, 1937.	Very mild faucial lesion; positive swab; sore throat one week before admission.

sensitized community. There may be persons who are difficult to immunize no matter what effort is made for them. Despite frequent exposure some of these persons fail to get the disease. This raises the question whether there may not be a cell threshold for antitoxin, so that although antitoxin cannot be detected in the blood it immediately appears when the appropriate antigenic stimulus is present. Then there is the type of person who cannot be immunized and suffers from diphtheria on more than one occasion.

The Occurrence of Diphtheria in Communities where Immunization has been Practised.

There is a definite tendency to consider that diphtheria does not occur in an immunized community. On seeing a child with a sore throat in our district medical practitioners have always asked the question: "Has this child been immunized?" On receiving an affirmative answer one has often felt reassured, perhaps falsely, that the condition is not due to diphtheria. This has been the experience also in a northern town where an outbreak of diphtheria of the *gravis* type occurred involving amongst others children who had been immunized. The appearance of the disease was so deceptive in this instance that for a time diphtheria was not thought of.

The occurrence of immunes who have lapsed is not generally realized. Dudley, May and O'Flynn[6] have found that the numbers of natural immunes may lapse to the extent of 3% in a short time. The lapse may be greater in the absence of appropriate reinforcement. Artificial immunes have been shown by Fraser and Brandon[7] to lapse to the extent of 34% in five years; but these children were found to respond rapidly to the administration of a further dose of 1·0 cubic centimetre of toxoid. The natural method of keeping immunity relatively permanent amongst both types of immunes is the existence of a carrier rate in the immune population sufficient to give an antigenic stimulus at intervals; for it has been found that without the administration of toxoid some of these immunes who have lapsed do not react to the Schick test, presumably because at the time a carrier rate was established in the community concerned.

In a population where there are approximately equal numbers of immunes and susceptibles it has been shown that an "immune's" chance of getting diphtheria may on occasions be as great as one-tenth of a susceptible's. Dr. Finger, medical superintendent of the Northfield Infectious Diseases Hospital, has kindly supplied me with figures concerning diphtheria in fourteen "immunized" persons and also with a description of the clinical condition of three patients. His notes are printed *verbatim*.

Re "immunized" children who have been infected. Of over 700 diphtheria patients during the past thirteen months, fourteen have had something to do with anatoxin. These facts may be summarized thus:

Clinical Condition.	Three Injections More than Three Months Before Admission.	Injections Incomplete.	Three Injections but Less than Three Months Before Admission.
Moderate faucial diphtheria	2		
Mild faucial diphtheria ..	1	1	2
Mild nasal diphtheria ..	1		
Technical cases uninvestigated (contacts and carriers)	5	1	
Technical case proved to be avirulent	1		

In regard to the patients in the first column, I should like to have investigated all these fully, but we have been able to complete tests on one only. In this case the organisms were definitely mitis type. The following are three histories of patients included in the first column.

D.C., aged five years, had received three injections of anatoxin, finishing in August, 1936. Admitted to hospital March 31, 1937, with history of five days' sore throat and one day husky voice. He was not very toxic-looking, temperature 98·8° F., pulse 100 per minute, firm whitish membrane over tonsils and spreading over anterior pillars to the uvula, quite inactive appearance. Given 12,000 units D.A.T., membrane cleared up completely in five days, having been of particularly adherent type. Chest clear. No complications. Organisms not typed. No Schick test performed.

M.A., aged one year and eleven months, had received three injections of anatoxin a year before admission on April 23, 1937. History of "cold" in head for a week, coughing and vomiting. Temperature 99·4° F., pulse 150 per minute, miserable appearance. The tonsils were grossly enlarged and inflamed, with definite membrane on both and on uvula. Given 30,000 units D.A.T., after which membrane cleared in two days. Cervical adenitis eighteenth day. Organisms not typed. No Schick test performed.

A.C., aged five years, had had three injections of anatoxin about a year ago. She was admitted to hospital on July 19, 1937, with history of sore throat for two days. Her temperature was 98·4° F., pulse 90 per minute, and she had a very small amount of loose membrane on the left tonsil. She was given 2,000 units of D.A.T. and made a rapid recovery. The organisms have been proved to be of the mitis type. She was not Schick tested.

The first two patients had moderate local lesions, but at no time while under our observation were the children concerned very sick. The last child was not noticeably ill.

It has been shown that an immunized person has at least twice as much chance of surviving an attack of diphtheria as compared with an unprotected individual; that is to say, the proportion of deaths recorded has been shown to be in some instances as high as 1:2; but in the majority of cases the balance has been even very much more greatly in favour of the immunized.

Methods of Artificial Immunization.

1. Toxin-antitoxin has dropped out of favour and is seldom used now.

2. Toxoid antitoxin in the form of floccules gives few unpleasant after-effects and is particularly suitable for administration to adults and those who react strongly to the Maloney test.

3. Alumina-activated toxoid is much the same as alum-precipitated toxoid.

4. Alum-precipitated toxoid is the substance that is used for the single inoculation method. There is considerable evidence accumulating that up to the present the one injection method does not give such lasting results as the ordinary anatoxin. Bousfield[8] has recently stated that only 37% of several hundred children originally Schick-positive were found not to react to the Schick test three months after receiving 1·0 cubic centimetre of alum-precipitated toxoid. He considers that the Ministry of Health should advise the discontinuance of the one-injection method. The difficulties associated with alum-precipitated toxoid consist of the undesirable reactions, common in any but young children, and the difficulty of concentrating the antigen in an appropriate dose of the substance. Recently Pope and Smith[9] and Jensen[10] have shown that this can be done. Many of the reports given of the conversion rates following prophylactic injections of antigen have been based on Schick tests done within three months. When the period has been over twelve months the relative permanence has not favoured alum-precipitated toxoid. Topley and Wilson[5] state that "there are records that indicate the wisdom of suspending judgement until we have had far more extensive experience" with this substance.

5. Löwenstein's administration of toxoid by inunction[5] is another method that has been used.

6. Formol toxoid is effective when administered by the intranasal route (Lesne *et alii*, 1927; Hosmer-Zambelli[5]).

7. In the combined method of Jensen[11] the injection of purified toxoid precipitated by aluminium hydroxide is followed by intranasal instillation of a purified toxoid dilution. The efficacy of the intranasal methods has been questioned by Dungal,[12] but the principle appears to be that once a primary sensitization has been established the strength of the secondary stimulant need not be great to produce a response. On the same argument reinforcement of the stimulus can be produced at will whenever danger of infection exists. This is just the scheme Jensen has in mind.

8. Anatoxin is the material most used in the Commonwealth, and under the arrangements existing for the supply of antigen to local boards of health in this State it is the only material available. I have spoken above of the desirability of spacing inoculations at intervals of five weeks to give the desired impetus for the production of antitoxin at the correct time. Any immunity that is developed may in a few instances fall below Schick level in three months after the last inoculation; but there is every evidence that a good foundation has been laid which may be built upon rapidly when the need arises. The fall that occurs after the maximum titre is reached can be described by the equation for a bimolecular reaction.[6] The constant in this equation varies with the individual. Jensen calculates that on this basis the duration of effective immunity after active immunization may vary from a few weeks or months to sixty years or more.

The Time for Immunization.

Since the most efficient conversion rates are obtained when the chances of primary sensitization are greatest, the best time to immunize is after the season of greatest carrier rate. This is usually after the winter; but difficulties of organization in this city make it more convenient, besides nearly as effective, to conduct the campaign at the beginning of the school year. Our experience in Hindmarsh, following a period of high carrier rate, tends to support these statements with actual results in the field. At present there are 1,229 children who have received three doses of anatoxin as well as over 100 others who have had one or two inoculations. We have been particularly careful to treat as many of the pre-school children as possible, and, based on the birth rate for the district, it appears that about one-third of the children of this age have been immunized. The population on December 30, 1936, was approximately 13,100. The average birth rate inside the district was 204·6 *per annum* for the last five years. From July 1, 1936, to August 19, 1937, there have been eleven cases of diphtheria; but none of the patients was an immunized person, and over 50% of them were adults. The average annual incidence of diphtheria for the last five years is thirty-four cases. Even when diphtheria is rife in the metropolitan area it cannot be said that the immunization of a proportion of the population has resulted in any immediate or increased risk to the unprotected portion. Further, there is little evidence that the protection given to those young children who are looked upon as most susceptible has been unavailing.

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THE TYPES OF CORYNEBACTERIUM DIPHTHERIÆ PREVALENT IN VICTORIA AND THEIR CLINICAL SIGNIFICANCE.[1]

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ALTHOUGH many present will be familiar with the work describing the typing of diphtheria bacilli, I shall briefly review, for the sake of those who have not had time to follow up this section of the literature, the events which led up to the investigations which have been made during the last six years.

The diphtheria bacillus was first adequately described by Klebs in 1883 in preparations made from false membranes and stained with methylene blue. It was isolated and thoroughly studied by Löffler in 1884, and his culture medium (a coagulated mixture of serum and glucose broth) is still used in routine work. The ætiological rôle of the bacillus was proved by the work published by Roux and Yersin in the years 1880 to 1890; for they demonstrated the production of an exotoxin and produced paralysis experimentally. They recommended the laboratory diagnosis of the disease by the demonstration of the characteristic bacillus.

Von Behring's work on antitoxin, published in 1890, made serum therapy possible, and this procedure soon became universal. Apart from the introduction of the Schick test to determine susceptibility and the introduction of methods for active immunization, very little further of importance with regard to diphtheria or the diphtheria bacillus had appeared up to the year 1930. Most bacteriologists accepted the original description of the bacillus and considered it to be of one type, making due allowance for a marked tendency to pleomorphism. Looking back into the literature and viewing it in the light of recent knowledge, one notes that Hammerschmidt, in Germany, described some strains of the bacillus giving a granular growth in broth, which were associated with a faucial and purely toxic type of the disease, whilst other strains gave a diffuse type of growth in broth and gave rise to a laryngeal and spreading type of disease.

In 1928 Parker had described some differentiation of colonies on tryptic digest media, but type differentiation as we now know it was commenced in 1930 by the staff of the Fever Hospital at Leeds, and the result was reported by Anderson, Happold, McLeod and Thomson. About that time a number of patients with diphtheria of unusual severity had been admitted to hospital and had failed to respond to the ordinary antitoxin treatment. A similar occurrence had been reported from Berlin during the years 1927-1929. The Leeds workers had been using a tellurite medium for the purpose of isolation and finally proposed a special medium consisting of chocolate tellurite agar made from a meat infusion prepared at a low temperature and filtered. On this medium, now often called McLeod's medium, it was found that in most cultures there were colonies of one or other of two clearly different types and that there was a definite correlation between the type and the clinical severity. The types were accordingly called *gravis* and *mitis*, the former being associated with clinical severity and a high case mortality rate, the latter (*mitis*) with mild cases and a very low case mortality rate. A few cultures at the time did not conform to these two types and the next year a third type, the "intermediate", was described by the Leeds investigators. The fact that the lack of response to antitoxin treatment in the case of *gravis* infections had been specially stressed caused Parish, Whatley and O'Brien, of the Wellcome Laboratories, to undertake an immediate investigation of the toxins and antitoxins of each type. Because their experiments with guinea-pigs and rabbits indicated that the prophylactic and therapeutic use of the ordinary commercial preparations were equally effective in protecting animals infected with *gravis* or *mitis* strains, and because *mitis* strains proved quite as toxinogenic *in vivo* and *in vitro* as *gravis* strains, they stated that their results were at variance with those obtained at Leeds. It should be noted, however, that at Leeds the observations were made chiefly on the clinical disease in the human being and not on animals. Parish, Whatley and O'Brien concluded that what appeared to be true for the Leeds area was not applicable to the country generally and said that the position called for the examination of a large number of serial cases in different areas. Since 1932 such examinations have been made and the great majority appear to have confirmed the original findings of the Leeds workers, although in one or two investigations the results seem to be of doubtful confirmatory value. Further work in Leeds in 1933 confirmed the importance of *gravis* strains; for in an examination of over 500 cases 70% were *gravis* and there was a 13% mortality, whilst among 100 *mitis* cases there were no deaths. The evidence accumulated in other areas, from 1931 to 1935, has recently been reviewed by Cooper, Happold, McLeod and Woodcock (*Proceedings of the Royal Society of Medicine*, July, 1936), and this clearly indicates that the results obtained in Leeds have been confirmed in other parts of Great Britain and in Ireland and also in some European countries. From data gathered in these areas they estimated that among 5,794 cases of clinical diphtheria the *gravis* type was responsible for a death rate of 13·3%, "intermediate" 8·6% and *mitis* 2·3%. I think it may be assumed, therefore, that the results originally obtained at Leeds have been confirmed elsewhere, though in some districts, particularly in Scotland, a number of atypical strains have been isolated, some of them being like *gravis* in most respects, but differing on account of their lack of ability to ferment starch or because of their avirulence.

[1] Read at the fifth session of the Australasian Medical Congress (British Medical Association), August, 1937.

In the light of these results from abroad it is of interest to examine the position in Australia. At the end of 1935 one or two medical practitioners in the Seymour district of Victoria reported some severe cases of diphtheria not responding well to early treatment with antitoxin. Examination of swabs sent to the Melbourne University bacteriology department indicated the presence of *gravis* strains in the district. This was the first report of the presence of *gravis* strains in Australia. Earlier in 1935 Anderson, Goldsworthy and Ward had begun an investigation of the types responsible for the more severe cases of diphtheria treated at the Royal Alexandra Hospital for Children, Sydney. These investigators reported on 184 clinical cases of diphtheria, of which 88 were due to infection with the *mitis* type, with a case mortality rate of 7·9%, while 96 were due to infection with the *gravis* type, with a case mortality rate of 26%. The malignant and submalignant cases were more frequent in the *gravis* type of infection. In these cases the death rate was unusually high, and it may be admitted that there was some selection of the more serious cases. Nevertheless the clinical significance of infection with *gravis* types is strongly emphasized. In that investigation no "intermediate" strains were isolated.

Investigations undertaken in Victoria during 1936 and 1937 indicate that the "intermediate" is the predominant type in clinical cases in the Melbourne metropolitan area and in some country districts, and suggest that the distribution of the various types in the population at large differs appreciably from that found in clinical cases. For example, in the study of 140 cultures obtained from 6,666 apparently healthy school children in a Melbourne suburban area, *mitis* strains were most common, constituting approximately 61%, whilst "intermediate" and *gravis* constituted 36% and 3% respectively. A large number of both *mitis* and "intermediate" strains were avirulent. Within a few weeks of this test in schools, cultures from fifty clinical cases of diphtheria were obtained through the courtesy of Dr. McLorinan, of the Fairfield Infectious Diseases Hospital, who also supplied case histories. This hospital receives patients from the Melbourne area, including the suburb in which swabs from the school children had been obtained. It was found that "intermediate" strains predominated in the clinical cases, being responsible for 50% of them, while *mitis* and *gravis* were each responsible for 25%. The case histories showed that the *gravis* type was more commonly associated with malignant diphtheria and there was evidence to show a comparatively poor response to antitoxin treatment in some cases.

A comparison of the results of the typing of cultures from apparently healthy school children with those from clinical cases suggests that in the human being *mitis* strains are common, but are of comparatively low virulence, probably often giving rise to subclinical infection and sometimes to a mild clinical infection; they no doubt serve a valuable purpose in immunizing the general population.

A point of considerable interest that has arisen from the local investigations is that in addition to non-virulent strains of *mitis* which are commonly met with elsewhere, we have encountered a large number of non-virulent "intermediate" strains which are apparently very rare in Great Britain—so rare that some English workers consider that it is not worth the expenditure of the time and money necessary to perform a virulence test when an "intermediate" strain is isolated.

With regard to the greater part of the State of Victoria, there appears to be a definite localization of types causing clinical cases. The *gravis* type appears to have persisted in northern districts round Seymour and has recently given rise to cases at Swan Hill and at Mulwala, just over the Murray River. In the latter outbreak reports indicate a severe type of the disease with a death rate which is considerably higher than the average and in some cases there has been a poor response to antitoxin treatment. At the neighbouring town of Yarrawonga, where children have been artificially immunized, no cases have occurred.

In 1936 there was an outbreak of diphtheria in a township near Ballarat where "intermediate" was the infecting type and where the clinical symptoms were severe. It was found necessary to close the schools for a period and the public mind was awakened to the need for artificial immunization.

In recent months an atypical strain has been consistently isolated from cases in the Wimmera district. This strain is like *gravis* in its appearance on McLeod's tellurite medium and in phenol-red broth; but it fails to ferment starch. It is therefore similar to strains described as Type IV by Wright and Christison, who isolated a number of such strains from clinical cases of diphtheria in Edinburgh.

Such findings as this emphasize the fact that the distribution of the types tends to vary from district to district, and cultures from clinical cases tend to be chiefly of the *gravis* or of the "intermediate" type in any one area. In view of these facts it seems that the severity of diphtheria outbreaks and the death rate from the disease will vary according to the type of bacillus introduced into a population where only a small proportion of children have become naturally or artificially immunized. If a *gravis* strain is so introduced many cases may quickly occur in which toxic complications are common and antitoxin fails to save life, especially if there is the slightest delay in treatment. A study of the death rate per 100,000 of population in the States of Victoria and New South Wales over the last thirty-seven years shows a great increase during the years 1910-1924, and it is difficult to find any explanation more likely than that of the prevalence of more highly virulent types. In order to prevent any further waves of relatively high mortality, it seems imperative to emphasize the fact that the findings of the bacteriologist in determining the prevailing

type and the therapeutic use of antitoxin may often be too late to prevent serious consequences, and the widespread prophylactic immunization of susceptible children should be advocated as the only satisfactory method of dealing with the disease.

IMMUNITY STUDIES IN DIPHTHERIA.

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THE individual variation in diphtheria susceptibility is associated with the degree of sensitization of the antibody-producing mechanism and with the amount of antitoxin in the blood of normal individuals. Glenny has pointed out the significance in antibody production of the differences between primary and secondary response to extraneous stimuli; the former amounts to nothing more than sensitization of antibody-producing mechanism and slow production at a low level of concentration, and the latter, at any period after the primary response has been evoked, results in prompt and relatively abundant production. This work also indicated the absence of a definite correlation between immunity and the amount of circulating antitoxin, so that methods of titration (such as that introduced by Romer in 1909) could not be accepted as providing a true index of the degree of immunity, during primary response at least. The Schick test was evolved in 1913 by Michiels and Schick, and it provided a simpler means for determining the presence of antitoxin than the titration method.

This investigation is one which is concerned with the study of primary and secondary response in a group of susceptibles, some of whom have already been sensitized by extraneous natural stimuli, and others of whom have no evident immunity. The reaction to injection of skin test anatoxin has been used to determine these groups, and observations are given which may indicate its reliability and also establish a criterion of positiveness for its interpretation.

Methods and Material.

The Schick Test.

The diphtheria toxin used was that supplied by the Commonwealth Serum Laboratories, Melbourne. It was supplied diluted ready for use in ampoules of ten cubic centimetres, and it contained sodium ethyl mercurithiosalicylate in a concentration of 0·01%. For work which had to be carried out away from the laboratory or clinic this product containing the new diluent was found to be more convenient in the maintenance of strict asepsis than the undiluted toxin contained in capillaries for solution in physiological saline solution.

Toxin to be used for the pseudo-Schick test was heated for ten minutes at 70° C., although if the special product is used it should be heated for a longer interval.

One dose of Schick toxin contained in 0·2 cubic centimetre was injected intradermally into the flexor surface of the left forearm, care being taken to produce a definite bulla by forcing the fluid into the dermis. Into the flexor surface of the opposite arm 0·2 cubic centimetre of the heated toxin was injected. Readings were made daily until the fifth day, when the differentiation could be made between the various reactions; and readings were continued subsequently so that further observations could be made on the nature and degree of response.

The Maloney Reaction.

For the Maloney reaction diphtheria formalinized anatoxin, supplied by the Commonwealth Serum Laboratories, was used. It was diluted 1 in 20, 0·3% phenol solution being added. A skin test dose of 0·1 cubic centimetre was injected intradermally into the flexor surface of the right forearm, in the same way as in the Schick test. Reactions were read after twenty-four hours and again after forty-eight hours if necessary. In the investigation which will be described this test was performed on susceptibles to the Schick test, and an attempt was made to establish a criterion for positiveness. Doses of prophylactic anatoxin were given on the same day as the reaction was determined.

The Investigation.

One hundred and five children, who were Schick reactors, were selected for detailed study of their antibody response to injections of prophylactic anatoxin.

In order to determine if any previous sensitization had occurred, each child was given an injection of 0·1 cubic centimetre skin test anatoxin into the dermis of the flexor surface of the forearm. Reactions were read after twenty-four hours and again after forty-eight hours if necessary. In this way it was possible, within the limitations of the Maloney test, to divide the series into Group A, having no reaction, and Group B, giving varying degrees of reaction and therefore furnishing evidence of previous sensitization.

Group A.

Members of Group A were given an initial dose of 0·5 cubic centimetre of anatoxin, and the Schick test was performed three weeks afterwards; if they were still reacting they received 0·75 cubic centimetre. A Schick test was again performed three weeks afterwards, and those proceeding to the third injection were given 1·0 cubic centimetre.

Group B.

In Group B were included all subjects showing any reaction to the skin test anatoxin. No criterion of positiveness was used and, as shown in Table I, four groups were arranged according to the nature and degree of their reaction. Dosage was estimated so as to establish a quantitative relationship with the degree of reaction. It will be seen that Groups III and IV would in the ordinary way be regarded as non-reactors to the Maloney test. The Schick

test was carried out three weeks after the first dose of anatoxin, and subjects who were still reacting were given the second dose.

TABLE I.

Group.	Nature of Reaction.	Anatoxin Dose in Cubic Centimetres.
I	Vivid flush of more than half an inch in diameter with central induration ..	0·01
II	Redness plus infiltration, approximately half an inch in diameter	0·1
II	Redness, less than half an inch in diameter ..	0·2
IV	Redness around the needle track	0·3

In Group I the dosage usually recommended is three injections of 0·01 cubic centimetre. In this case, however, the dose for the second injection was increased to 0·1 cubic centimetre for the majority of subjects, and a small control group received 0·01 cubic centimetre. In Group II subjects, dosage for the second injection was varied from 0·2 cubic centimetre to 0·7 cubic centimetre, and observations were made three weeks later on the establishment of immunity.

Group III subjects, still susceptible after the initial dose of anatoxin, were given doses from 0·5 to 0·75 cubic centimetre, and the Schick test was performed three weeks later. Group IV reactors after their first injection were given the full 0·75 cubic centimetre second doses, and the Schick test was performed at the usual time.

All members of Group B, still giving a reaction to the Schick test after the second injection, proceeded to their third dose of anatoxin as shown in Table III.

Results.

Examination of Table II shows that in Group A (giving no reaction to skin test anatoxin), 59 subjects were included. Sixteen (27·1%) became non-reactors to the Schick test after the first injection of 0·5 cubic centimetre of anatoxin, and another 38 (64·45%) became non-reactors after the second injection of 0·75 cubic centimetre, so that 91·55% of children, as determined by the Schick test, were immune after two injections. Five subjects (8·45%) proceeded to their injection of 1·0 cubic centimetre. These results do not compare unfavourably with those of Martin, Loiseau and Laffaile (1928), who obtained 37% of non-reactors to the Schick test after the first injection, and 98% of non-reactors after the second injection.

TABLE IIIA.

Thirty-Six Reactors to the Maloney Test.

Time.	Non-Reactors to the Schick Test.		Group.	Number.	Dose. (Cubic Centimetres.)
	Number.	Percentage.			
Three weeks after the first injection.	20	43·3	I II III IV	8 6 5 1	
Three weeks after the second injection.	16	34·78	I (10)	8 2	0·1 0·01
			II (2)	1 1	0·2 0·5
			III (3)	2 1	0·5 0·75
			IV (1)	1	0·75

TABLE IIIB.

Ten Reactors to the Maloney Test.

Reactors to the Schick Test Three Weeks after the Second Injection and Proceeding to the Third Injection.		Group.	Number.	Second Injection. (Cubic Centimetres.)	Third Injection. (Cubic Centimetres.)
Number.	Percentage.				
10	21·73	I (3 subjects)	3	0·1	0·1
		II (2 subjects)	1 1	0·7 0·3	1·0 0·3
		III (3 subjects)	2 1	0·5 0·6	0·75 1·0
		IV (2 subjects)	1 1	0·75 0·75	1·0 1·0

The large percentage in this group becoming non-reactors after the second inoculation provides evidence, first, of a satisfactory response of the antibody-producing mechanism to initial extraneous stimulus, and, secondly, of a prompt and abundant rise in antitoxin level after the second injection. A large number of these children becoming negative after the second dose of anatoxin presented well-marked local anatoxin reactions after injection; and in view of the fact that they had been non-reactors to the Maloney test the evidence would tend to support Dwyer's observation of the appear-

TABLE II.

Subjects.	Reactors to the Schick Test. (105)		Maloney Test.			
			Group A. Reaction Absent. (59)		Group B. Reaction Present. (46)	
	Number.	Percentage.	Number.	Percentage.	Number.	Percentage.
Non-reactors to the Schick test after the first injection	36	34·3	16	27·1	20	43·3
Non-reactors to the Schick test after the second injection	54	51·4	38	64·45	16	34·78
Reactors to the Schick test after the second injection, proceeding to the third injection	15	14·3	5	8·45	10	21·73

ance of local reactions at this stage of treatment. Another point which must be considered in view of Glenny's work is the possibility of a preexisting sensitization not revealed by the Maloney reaction in these children, so that the first injection of anatoxin brings about not a primary, but a secondary response.

Examination of Table II shows that in Group B 46 subjects were included who were giving some reaction to the injection of skin test anatoxin. Twenty (43·3%) were immune to the Schick test after the first injection of anatoxin, and 16 (34·78%) were immune after the second injection, so that 78·08% were immune after two injections. Ten (21·7%) proceeded to the third injection.

In interpreting these results it must be remembered that Groups III and IV, who had received an initial dose of anatoxin, would ordinarily be regarded as having no Maloney reaction and would be given full first doses of 0·5 cubic centimetre. It must also be remembered that in this experiment the second dose was varied, so that observations on the nature of secondary response to artificial stimuli could be made. The former will be best understood by reference to Table III.

The large proportion of subjects (43·3%) becoming non-reactors to the Schick test after one injection of anatoxin provides evidence of previous sensitization by natural stimulation of the antibody-producing mechanism. It also demonstrates the significance of Glenny's observation on primary response, that non-apparent sensitization may exist with a level of antitoxin in the blood insufficient to prevent a reaction to the Schick test. It seems reasonable on these grounds to regard susceptibles giving a response to the Maloney reaction as being in a state of primary response, and when the reaction belongs to the Group I or II type, justification probably exists for leaving them. Infective or subinfective doses of *Corynebacterium diphtheriæ* will produce in these groups a rapid response of the secondary type, with prompt and abundant production of antitoxin.

The number of subjects becoming "Schick-immune" after the second injection is small compared with the results obtained in Group A. Of ten subjects in Group B proceeding to the third injection, five belonged to Groups III and IV, with a total of fifteen subjects, and five belonged to Groups I and II, containing thirty-one subjects. It would appear that the initial dose for Group IV and also to a less extent for Group III was too small to evoke a satisfactory response; and in view of the results obtained for Groups I and II this would suggest that Groups III and IV, for purposes of artificial immunization, should have been regarded as non-reactors and given full initial doses of 0·5 cubic centimetre. The variation of the second dose for experimental purposes was also probably responsible for the results obtained.

The nature of antibody response to second injections in this group would also seem to vary. In the table it will be seen that in Group I eight subjects receiving 0·1 cubic centimetre for a second injection and two subjects receiving 0·01 cubic centimetre became immune, while three receiving a dose of 0·1 cubic centimetre were still reactors to the Schick test. In Group II, two subjects receiving 0·2 cubic centimetre and 0·5 cubic centimetre respectively became immune, whereas two subjects receiving 0·3 cubic centimetre and 0·7 cubic centimetre were still reacting to Schick toxin three weeks later. Examination of Group III reveals that three subjects were "Schick-negative", two receiving 0·5 cubic centimetre and one 0·75 cubic centimetre, and that three were still reactors, of whom two had received 0·5 cubic centimetre and one had received 0·6 cubic centimetre of anatoxin. In Group IV, one subject did not react to the Schick test after receiving 0·75 cubic centimetre, whereas two subjects were still reacting after the same dose.

Discussion.

The group of subjects handled is small, but it is considered that the results obtained demonstrate something of the nature of primary and secondary response to artificial stimuli in susceptibles with no immunity reaction, and also of the same responses in subjects in whom a primary response has been evoked by natural causes.

The results in general for Group B suggest a difference between the antibody response to anatoxin and the antibody response due to natural stimuli. It seems easier, for the most part, artificially to immunize subjects who respond to the Schick test but give no reaction to skin-test anatoxin. On the other hand, as pointed out before, justification appears to exist for leaving members of Groups I and II of the general group of those reacting to the Maloney test. The absence of local and general reactions in the non-reactors after the first injection of prophylactic anatoxin would indicate a satisfactory degree of reliability for the Maloney test. The reactions described in the third and fourth groups of the general Group B must indicate some degree of previous sensitization, because local reactions were invariably observed after the first injection of immunizing anatoxin. It is the opinion of the writer that the reaction in these groups should be regarded, not as "negative" in the sense it implies, but only as indicating the necessity for full initial doses of anatoxin. The fact that individuals in the complete susceptible Group A became immune after the first injection of anatoxin suggests that the primary response to the same stimulus is greater in some individuals than in others; or, on the other hand, that the Maloney reaction does not always indicate the existence of a state of sensitization. Dwyer has drawn attention to the fact that the Maloney reaction develops *pari passu* with immunity, although this is not invariable. The dosage usually recommended for susceptibles giving a reaction of the Group I type is three injections of 0·01 cubic centimetre of anatoxin at three-weekly intervals. In this group, it will be seen that the second injection for subjects becoming

immune was 0·1 cubic centimetre in eight instances, and 0·01 cubic centimetre in two, and that two subjects receiving 0·1 cubic centimetre proceeded to the third injection. No untoward reactions were observed in those subjects receiving the increased dose, but the numbers are too small to give conclusive evidence, and some people are hypersensitive.

Delayed reactions to the skin test anatoxin, as described by Underwood, were not observed in any member of this series.

A Comparison of the Pseudo-Schick and Maloney Reactions.

As every member of this series received heated Schick toxin as a control at the time of Schick testing, and subsequently received skin-test anatoxin immediately before immunization, it was possible to make comparisons between both reactions in the same individual. Dwyer has drawn attention to the fact that as far as is known it is doubtful whether the pseudo-reaction can replace the Maloney test. On the other hand, Mitman states that the intradermal toxoid test of Maloney and Zoeller corresponds exactly with the pseudo-response in the Schick test. The results obtained in this investigation support the former contention, for of one hundred and five children examined, agreement in result was obtained in only 77 cases, or 73·3%. Of the 28 subjects whose tests did not agree, 22 giving no control reactions to the Schick test gave a reaction to the Maloney test, and six giving control reactions gave no reaction to the Maloney test.

It would therefore appear that the Maloney reaction is a safer indication of previous sensitization than the pseudo-reaction.

Conclusions.

The reactions in human subjects to the injection of diphtheria toxin for Schick testing and of skin-test anatoxin provide very valuable data for determining immunity, but at the same time, when these tests are being interpreted, it is important to realize their limitations. Antibody response, either primary or secondary, to natural or artificial stimuli, is subject to considerable variation in nature and degree. Knowledge of the factors which may influence the antibody-producing mechanism is still incomplete. It seems most likely that the response to extraneous stimulation is the predominating one, but much as yet remains to be learned of the possible importance of genetic and evolutionary factors in determining the antibody level of the blood of human beings.

Summary.

1. The significance in antibody production of the difference between primary and secondary response and the relation between immunity and the level of concentration of circulating antitoxin have been discussed.

2. Methods and material have been described.

3. An investigation has been carried out of 105 reactors to the Schick test with regard to the nature of their primary response to extraneous and natural stimuli, and to that of their secondary response to artificial stimulation of the antibody-producing mechanism.

An experimental classification has been given of reactions to the injection of skin-test anatoxin, and an attempt has been made to establish criteria of positiveness.

The determination of anatoxin efficiency in both Maloney reactors and non-reactors has been discussed.

Observations have been made on anatoxin reactions, especially after second anatoxin injections.

4. A comparison of the pseudo-Schick and Maloney reactions is given.

5. Conclusions have been drawn.

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THE USE OF MOULDS AND SURFACE APPLICATORS IN RADIUM THERAPY.

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GREAT advances have taken place in therapeutic radiology during recent years, and in both radium and X ray therapy perhaps the most notable feature

in the development is the greater complexity of methods of application. Of recent years, too, it has become apparent that there is a tendency to replace interstitial radium therapy, or implantation of radium into the tissues, by external radiotherapy. External radiotherapy includes: (i) X ray therapy; (ii) telecurietherapy, or the use of the radium bomb; (iii) surface radium therapy.

In deep X ray therapy results are now being achieved in types of malignant disease previously regarded as hopeless. A recent development has been that of contact X ray therapy, evolved by Chaoul, of Berlin, in which a concentrated fractionated dose is given at low kilovoltage and very short focal skin distance with a specially constructed X ray tube. It must not be lost sight of that this method was brought forward in Germany because of the shortage of radium in that country and as an alternative method of treatment of surface lesions, particularly of the lip, mouth and skin. The results reported so far are very promising; but the use of the method is limited to the treatment of rather superficial lesions. The necessity for daily treatment over a long period, which is essential to the technique, is somewhat of a disadvantage in practice.

The radium bomb is giving quite spectacular results at several large radiotherapeutic centres, especially in carcinoma of the mouth and the upper part of the respiratory tract; but the great expense involved makes this method uneconomical and prohibitive excepting when large amounts of both money and radium are available.

The object of the present paper is to draw attention to a branch of γ ray therapy which, while not new in principle, has not received the recognition due to it in some cities.

In surface radium therapy radium is arranged on an applicator or mould fitted to the particular region of the body, at a distance from the surface which may be anything from a few millimetres up to five or six centimetres. The applicator or mould may be applied externally to the body or within such a cavity as the mouth. It is not proposed to deal at length with the use of unfiltered or lightly filtered radium plaques, except to condemn their wholesale use in malignant disease of the skin; but an account of some detail will be given of the methods of using specially constructed moulds or applicators depending for their action on γ radiation.

This type of γ ray therapy is applicable in a wide variety of cases, and in some situations will achieve results not possible by any other method. It has been placed on a much more scientific basis by the development quite recently of methods of calculation of radium dosage in terms of the quantity of radiation delivered, and not, as hitherto, in terms of milligramme-hours or millicurie-hours. These latter terms are not units of dosage in the true sense, and their use as such has resulted in too much inaccurate and ineffective work in the past.

We may apply the same number of milligrammes of radium for the same number of hours in two exactly similar lesions and yet the quantities of radiation delivered to the lesion may be widely different in the two cases. The factors of area over which the radium is distributed, the distribution of the radium containers, the distance of the radium from the skin, filtration of the radium containers, all must be considered. Apart from this there is the problem of variation of biological effective dose with the time over which irradiation is given.

At the Manchester Radium Institute, where a dosage system for γ ray therapy has been developed, the use of surface radium methods has increased as technique in the manufacture of moulds and applicators has improved. Because of certain advantages inherent in the method it is the practice, too, at that centre to choose the external irradiation method rather than interstitial implantation, when both appear equally suitable for the treatment of any individual lesion. The Manchester system of dosage is described in an article by Paterson and Parker.[14]

Surface γ ray therapy must continue to be of the greatest value, particularly in centres where no radium bomb is available yet relatively large amounts of radium or radon are at hand.

Historical.

The earliest efforts in radium therapy over thirty years ago were confined to the use of flat superficial applicators of the unscreened or partially screened type. It is most important to realize that this type of applicator or plaque (still used far too widely) should be used in the most superficial of lesions only. The greater part of the effect produced is due to β rays, which are effective at not more than a few millimetres below the surface. Finzi[10] has condemned their use in rodent ulcer. One need have no hesitation in saying that the results in malignant disease of the skin would be uniformly better if accurate γ ray therapy were to replace the wholesale use of lightly filtered plaques.

The introduction of a screen of heavy metal to filter out the less penetrating rays by Dominici in 1907 and the classical demonstrations of Wickham in 1912 set surface radium therapy on a firm footing, and this method came into use for cancer of the skin, lip and buccal mucosa.

Edling in 1918 introduced the use of dental plastic compound for the treatment of labial and intraoral lesions. Regaud[3] started using plastic moulds with radium at a distance from the skin in about 1919. In 1922 three of his colleagues introduced Columbia paste, a mixture of beeswax, paraffin and powdered wood, and this has since been used extensively at the Paris centre and elsewhere. Many other materials have since been utilized in the construction of moulds and applicators, the practical value of each material varying with the site, extent and type of lesion under treatment.

Stevens[4] has pointed out the great part that surface radium therapy has played in the successful

results obtained at such well-known clinics as the Radiumhemmet, Stockholm, and the Radium Institute, Paris.

Regaud[2] reported some years ago that the method had "resulted in great progress in the treatment of extensive and deep cancers of the skin, of the lips, and of the mouth (excepting the tongue), cancers of the pharynx, larynx, breast *et cetera*".

The interstitial implantation of radium needles was a much later development than surface radium therapy. It was first used in a more or less empirical way about fifteen years ago, and rapidly became popular. It remains today an invaluable method; but there appears to be a general tendency of late to reserve it for tumours in special situations. Regaud regards its use as limited, its chief value being in carcinoma of the tongue. Other lesions for which interstitial radium therapy remains in general use are some cancers of the skin, subcutaneous tissue, oral cavity, breast, and some secondary glands. It is also used in such organs as the bladder and rectum.

Many lesions seen at a large clinic can be treated by the implantation of radium. In very many of these, however, implantation will not be the method of choice, and in some it will not be successful however expert the therapist. Treatment by a mould or applicator is often preferable.

Materials Used in Moulds and Applicators.

Columbia Paste.

As mentioned above, Columbia paste was introduced in 1922 by three workers at the Paris centre. It was used quite extensively for some years; but it is by no means an ideal material for mould construction and has been largely superseded by lighter and more serviceable materials.

The wax is made soft by immersion in hot water and can then be moulded to the body. The old method of fixing the radium containers to the mould by heating them and embedding them in the wax must be condemned as too inaccurate. It is advisable to drill grooves for the needles, measuring the distance from radium to skin by means of calipers.

Columbia paste has been used for external radium applications of rather large dimensions in the treatment of secondary malignant glands of the neck, lesions of the chest wall, and malignant growths of the face and head; but when a radium-skin distance of several centimetres is demanded by the depth of the lesion below the surface, its use would mean a very heavy unwieldy mould and consequent discomfort to the patient. Added to this very real disadvantage is the fact that this substance does not accurately take the shape of the affected region. Its use has been entirely discarded at the Manchester Radium Institute.

Dental Plastic Material.

Substances of the nature of dental plastic material were used in radium work as long ago as 1918. One of the best known is Stent's composition, or "Stent"; but there are others less well known that are equally as serviceable. Stent's composition can be used in the construction of external applicators of moderate size, about the face, head or extremities, and also intraoral moulds. The latter will be dealt with later.

For external moulds "Stent" is more easily worked than Columbia paste, and can be made to fit accurately to areas such as the ear and nose, to which Columbia paste could not be made to fit.

It is essential for accurate work that a plaster cast of the region to be treated be made, the "Stent" then being moulded to the cast. The "Stent" is built up to about half a centimetre more than the required radium-skin distance, and then grooves are made in the top surface for the reception of the radium tubes or needles, which are arranged according to definite rules. Grooving is best done by means of the ordinary dental drill. The distance from the bottom of the groove to the under-surface of the mould is measured by means of calipers.

For very accurate work the substance known as dental base plate may be used as the base of the mould, as it can be made to fit perfectly to a plaster cast of any lesion, however irregular. "Stent" is then used to build up the mould to the necessary distance. This type of mould is a useful one for research purposes, and the same method has been perfected at Manchester (as will be described later) for the construction of intraoral moulds.

"Nidrose."

"Nidrose", which is of French manufacture, has been used extensively at Brussels and Manchester for mould construction. Unfortunately it is rather expensive, even in England. It is of cellulose composition, is very light, and is readily moulded on a previously prepared plaster cast.

At the Manchester Radium Institute "Nidrose" is looked upon as the ideal material for the construction of large external moulds. It is put up by the manufacturers as a perforated meshwork material, and for this reason is particularly suitable for the treatment of large lesions of the proliferative ulcerative variety.

The technique consists first of all in the making of a plaster cast. The "Nidrose" is heated between electric hot plates and then the technician, wearing heavy gloves, presses it down while still soft over the irregularities of the cast. During the moulding the meshwork of the material is opened out, and this forms one of its distinct advantages, as it allows the passage of discharge in ulcerated growths.

The "Nidrose" gradually hardens on exposure to cool air, and when hard it can be trimmed by wire-clippers and if necessary the central part can be cut away.

In large "Nidrose" moulds the radium-skin distance is usually several centimetres, and at Manchester this distance is obtained by the attachment of ordinary corks to the meshwork by means of split pins. The radium tubes are enclosed in an

ordinary rubber tube resting on the corks. Paterson and Parker[14] have shown that the ideal arrangement of radium on a mould is in the form of a circle, and if the ratio of the diameter of the circle to the radium-skin distance is 2·83, homogeneous irradiation will be obtained over the area being treated when all the radium is arranged uniformly round the circle with none in the centre. When the ratio is more than 2·83, a percentage of the radium must be placed inside the circle. The rubber tube containing the radium is therefore generally arranged as a circle or ovat.

"Nidrose" moulds may be used in the treatment of moderately sized or large lesions of the head, face and neck, and for malignant glands or deeper lesions in the neck, as carcinoma of the larynx. Here a radium collar is constructed, that is, a ring of radium entirely surrounding the neck. A cylindrical mould of this substance may be used for carcinoma of the penis and malignant lesions of the arm or leg.

Adhesive Material.

At the Manchester Radium Institute the use of radium plaques in the treatment of malignant disease of the skin has been almost completely superseded by the development of an adhesive applicator for radon seeds or needles. This had been described in an article by Johnstone.[16]

The material used is "Elastoplast" felt, which is adhesive on one surface, and in its usual form is 0·5 centimetre thick. A piece of felt of an appropriate size is cut out and stuck on the skin over the lesion; the piece should be about one centimetre wider in all diameters than the area to be treated. If the lesion projects above the surface a central hole can be cut in the felt to accommodate it. The felt is then built up in one, two or more layers to the appropriate distance.

Radium or radon containers are then arranged on adhesive plaster, the distribution of the containers being appropriate to the size of the area and to the radium-skin distance. The plaster is then inverted on the felt and kept in position by more plaster. If radon needles or seeds are used it may not be necessary to admit the patient to hospital.

This is a very useful method for the treatment of small or moderately sized rodent ulcers and squamous epitheliomata of the skin of the face, head and body generally (including small epitheliomata of the edge and posterior aspect of the pinna), skin recurrences about the scar after amputation of the breast for carcinoma, nævi in children, and keloids.

For malignant lesions the adhesive applicator is generally applied continuously for seven or eight days, and the dose in γ r units and the radium-skin distance adjusted according to the type of neoplasm and the depth of infiltration.

For nævi and keloids, doses are kept very much smaller, and the treatment is repeated at intervals of two or three months till the desired result is obtained. The use of mild doses of γ rays in the treatment of nævi has been emphasized by Finzi, and he particularly deprecates the use of carbonic acid snow or caustics of any sort.

The cosmetic results from this form of γ ray therapy are excellent, provided the doses are carefully chosen. The method is particularly suitable for the treatment of out-patients with small rodent ulcers and epitheliomata about the face. I use silver radon seeds for this purpose.

For the treatment of lesions in such regions as the inner canthus of the eye the method is not recommended. Here implantation of needles or gold radon seeds should be used in preference.

Sponge Rubber.

Sponge rubber can be obtained in rectangular blocks, or in tubular form with a small central lumen. It is a useful substance for the external application of radium, having the advantages of lightness and comfort. In the absence of "Nidrose" it can be used for treatment to the neck (in the form of a pack or a collar), breast, or other large area. It differs from other materials described above in that it cannot be moulded rigidly to the part under treatment, but has to be strapped in position. Radium needles are attached to the surface of the rubber.

A cylindrical mould of this material has been described by Hutchison[15] for the radium treatment of epithelioma of the penis, radium needles being fixed to the outside of the rubber by adhesive plaster, and the whole strapped to the abdomen and thighs. A penis mould may also be made of moulded wax or "Nidrose". By means of an applicator of this nature a more or less homogeneous dose can be given through the whole shaft of the penis. Hutchison has reported good results from this method, the outstanding advantage over surgery being that the penis is retained. Hutchison also notes that the erectile function of the organ is commonly retained after radium therapy. Thomson Walker[7] advocates irradiation as the treatment of choice in cancer of the penis.

Since Hutchinson's article was written ten patients who had had epithelioma of the penis (proved by biopsy) have been shown at a clinical meeting at Manchester; all had been treated by a radium mould only, and all had been clinically free of malignant disease for periods up to two and a half years.

Tubular sponge rubber can be used for holding radium tubes in such sites as the rectum or nasal cavity, the advantage over ordinary rubber tubing being that the radium is kept at a definite distance from the mucosa.

Other Materials.

Maino[5] has used hygroscopic cotton soaked in paraffin, and finds it clean and light and easily adaptable to any part of the body. Others have used celluloid, wood or plaster.

A material, to be suitable for mould construction, should retain a rigid position, in close contact with the lesion, and should contain no metal which might give rise to secondary soft radiation.

Mouth Moulds.

The use of moulds in oral cancer is limited to the treatment of lesions on the less mobile parts, namely, growths of the palate, the alveoli, the buccal surface of the cheeks, and the anterior part of the floor of the mouth. For convenience, the lip will also be considered here, as at this situation moulded applicators have been used with great success for many years, particularly on the Continent.

Much has been written by Grier[8] and others of the treatment of malignant disease of the mouth by the contact application of radium, in which the latter is clamped over the growth by special clamps or by lead bands; but an applicator made to fit like a dental plate is undoubtedly better, because of the certainty of keeping the radium at the required distance from the surface.

Every case of cancer of the mouth should be considered on its merits, and the most suitable therapeutic technique selected. Interstitial implantation will often be found to be the method of choice; but the more thoroughly conversant with the technique and adaptability of moulds one becomes, the wider their field of application will be found to be.

At the Manchester Radium Institute surface radium therapy occupies a very important place in the treatment of intraoral cancer. Formerly it was the practice at that centre to use vulcanite for intraoral moulds; but this has been replaced by a method in which a double layer of dental base plate is used as the base of the mould, and this is surmounted by a mass of "Stent" in which the radium is placed. This was found to be more economical and less laborious.

Before treatment is undertaken it is wise to remove any foul and septic teeth; but certain teeth, giving no obvious trouble, especially in the vicinity of the growth, are better retained, as they serve as an anchor for the mould.

In the technique of manufacture of the mould the first step is the taking of an impression by the usual dental method, from which a plaster cast of the lesion and surrounding normal mucosa is obtained. Dental base plate is then moulded on this to a thickness of 0·5 centimetre. A softened block of "Stent" is then placed on the base plate, the whole placed in the mouth, and an impression obtained from the other jaw on the soft "Stent". The radium needles are placed in grooves drilled in the "Stent" on the surface in contact with the base plate, and the "Stent" and base plate then fused together at the edges. In this way the radium-mucosa distance is made uniformly 0·5 centimetre.

Recently, at Manchester, black tray compound has been substituted for "Stent" for this purpose.

With an aim at the ideal of homogeneous irradiation throughout the whole tumour zone, the growth whenever possible should be sandwiched between the intraoral mould and an external applicator. In lesions of the lip this can be done by means of an external mould of base plate or "Stent" joined to the inner mould by a bolt; radium is then mounted on each side of the lesion. In lesions of the cheek, near the angle of the mouth, a similar method can be used.

In epitheliomata of the anterior part of the floor of the mouth the intraoral mould is of the type described, and the external applicator may be of "Nidrose", the radium being at such a distance from the skin that there is an effective dose from the floor of the mouth right through to the submental region.

Advantages of Surface Gamma Therapy.

There are several advantages in the method of applying γ rays at the surface. In the first place, it does not involve an operation. This is a big factor from the patient's point of view. In the treatment of oral cancers in elderly patients, a general anæsthetic, either for radium implantation or excisional surgery, is not to be lightly undertaken, principally because of post-operative complications, such as bronchopneumonia. There is no such risk with radium therapy applied by a mould.

Secondly, homogeneous irradiation is obtained over the tumour zone more accurately with a surface mould than with interstitial implantation. This is of the greatest importance, as not only is there greater safety to the surrounding normal tissues, but all tumour cells are more likely to get the same dose. It is for this reason that the cosmetic results from surface γ therapy are as a general rule better than those from implantation for the same type of lesion. It is now being recognized by radiotherapists that for each type of tumour there appears to be a definite lethal dose which must be delivered to all cells of the tumour for its permanent disappearance. This dose will vary with the total period over which irradiation is given. Paterson[14] believes that "total dosage is the most important single factor in therapy provided due consideration is given to the duration of irradiation".

Experienced workers with radium agree that uniform distribution of needles or seeds is not always easy to obtain in implantation; in fact it is sometimes impossible. On a radium applicator radium containers can be accurately arranged according to definite rules of distribution, and by accurate adjustment of the radium-skin distance an effective dose can be delivered to the whole treated area, and at a required depth below the surface. When the tumour is situated between two surfaces a double mould, one on each surface, can be employed so as to achieve a uniform dose throughout the whole thickness of the tumour. Again, if the tumour is situated within a part of the body of cylindrical shape, such as the neck or one of the extremities or the penis, the whole part can be surrounded by a circular or cylindrical mould, and a uniform intensity of radiation given throughout the whole thickness of the part.

Thirdly, by surface application, satisfactory results will be obtained when implantation is impossible. Large deep lesions, close to bone, as in the face and scalp, are much better treated by this method.

In the fourth place, this method is of value in association with other methods. This has been emphasized by Cade.[6] It has been used to supplement implantation; for example, in the treatment of a tumour infiltrating to a moderate depth below the surface, a plane of needles can be inserted deep to the lesion to deal with the deeper parts, and surface irradiation can be added to provide homogeneity throughout the whole tumour. It has also been used in association with the insertion of radium in a cavity, as for instance a radium-carrying bougie with a radium neck-pack or collar for carcinoma of the upper end of the œsophagus.

Fifthly, it is possible, by means of surface moulds, to employ continuous treatment over a long period. From tissue culture experiments it has been concluded that a tumour cell is most radio-sensitive in the pre-mitotic phase. If this is so, continuous irradiation over a long period should be more efficient in causing death of the tumour than a shorter course, as cells will be irradiated during many successive mitotic periods. This argument for the superiority of protracted irradiation has, however, been questioned by McWhirter and others. Protracted irradiation is recognized as having an advantage over shorter, more intensive methods, in that lethal effects can be obtained on tumour cells with less damage to the normal tissues. It is therefore to be recommended for lesions in sites where the blood supply is relatively poor and the quantity of subcutaneous tissue relatively slight. Paterson, of Manchester, recommends treatment by radium moulds over two or three weeks for lesions of the distal parts of the extremities, especially for large epitheliomata of the dorsum of the hand. Radium necrosis was found to occur in a number of these cases in which treatment by shorter more intensive methods or by implantation had been used.

In the sixth place, Cade[6] gives as an advantage that there is no risk of tumour dissemination when radium moulds are used as there is with implantation. It is possible that this is not of great importance. Experimental work on animal tumours by various investigators has shown that whereas manipulation or massage of a tumour is a factor in the production of metastases, surgical treatment, that is, incision or excision, does not appear to have any appreciable influence.

Finally, treatment can be interrupted at intervals for the convenience or rest of the patient. This makes management and nursing easier. When a mouth mould is used the applicator can be worn for a few hours at a time and left out at meal times and during the night.

Criticism of the Method.

Chief among the criticisms usually offered is that of the time and trouble necessary in the preparation of the applicator. Of the more complicated moulds and applicators, this is, of course, true. It would appear, however, that this is more an argument in favour of concentration of radium work at large centres where the work can be better undertaken by those specially trained rather than a legitimate objection to the method. It is far better to restrict oneself if possible to one method of treatment, which, though difficult and time consuming, will produce permanent regression of the lesion, than to apply a less suitable method and be forced in a number of cases to treat a second or even a third time for recurrence or incomplete resolution of the tumour. Cutler[9] admits that the preparation of moulds is laborious, but says the "results fully justify the efforts".

Again, the critic may point to many failures in the past from this method. But knowledge and technique have improved enormously in the last decade; and past failures, particularly in the treatment of squamous epithelioma or rodent ulcer, if investigated, will be found capable of explanation as a rule on either of two grounds: (i) Insufficient dosage, which may be due to faulty construction of the mould, inaccurate measurements, lack of knowledge of dosage measurement or of the dosage which should be given; or (ii) unsuitability of the lesion for this type of therapy, either from site, depth of infiltration, or lack of tissue tolerance owing to previous inadequate radiotherapy. This really depends on "(i)", as the experienced therapist will be able to tell whether an adequate dose can be delivered to all parts of the tumour by means of a mould.

In no other department of radium therapy are greater care and accuracy necessary. H. E. Martin,[11] of the Memorial Hospital, New York, in a paper on the treatment of skin cancer by surface radium therapy, discusses radiation failures from this method as seen in patients at the time of their admission to his clinic. He states:

> Many skin lesions have been subjected to repeated irradiations over a period of months or even years with little radiation effect. No one should attempt radiation therapy even of basal cell carcinoma, unless he has the experience and courage to apply at one sitting a sufficient quantity to cause complete regression.

For much surface γ therapy to be undertaken, it is of course essential that a moderately large amount of radium (or radon) be available in tubes of suitable sizes and linear intensities. Herein lies another argument for concentration of radium work in big centres.

Essentials for the Success of the Method.

Essentials for the success of the method are as follows:

1. With certain exceptions, the mould or applicator should be made to fit each individual patient. Only by individual construction can perfect fitting and accurate dosage be obtained. It is essential that any applicator should retain its position exactly over the area under treatment all the time and also keep the radium exactly at the calculated distance from the surface. At the big radium centres there is generally a well-equipped laboratory for the construction of applicators for external treatment and for devising new methods of application. Mechanics are also specially trained

for this type of work. By this means new ideas are evolved.

2. The distribution of the radium on the applicator must follow definite rules.

3. A system of dosage measurement must be used. Murdoch and Stahel, of Brussels, have evolved a method of dosage measurement based on the quantity of energy, expressed in ergs, absorbed by each cubic centimetre of tissue. Sievert, of Stockholm, expresses doses in intensity-millicurie-hours. Failla and Quimby calculate doses in units of erythema. Paterson and Parker,[14] of Manchester, have produced a system of dosage which has stood the test of clinical use at the Manchester Radium Institute for over four years, and is simple enough to be applied in individual cases at a large clinic. In their system dosage is calculated in international *r* units of quantity of radiation, and it is also possible to estimate depth doses below the surface in the case of distance moulds, and "through and through" doses when a double or "sandwich" applicator is used.

Rules governing the distribution of radium on moulds and applicators have been dealt with by Sievert, Mayneord, Murdoch and Stahel, and others. Perhaps the most important part of the dosage system inaugurated by Paterson and Parker is that dealing with radium distribution, which has been reduced to a comparatively simple form, and the rules given by them can be easily applied in practice. By faulty arrangement of the radium on an applicator (and this applies equally well to faulty arrangement in implantation), it is possible to obtain overdosage in one part, leading to local radium necrosis, inadequate dosage in other parts, and other areas of approximately correct dosage; so that the net result is cure of portion of the growth, non-disappearance in another part, and high dose effects in another. Further radiotherapy will then lead to massive necrosis in the previously overdosed area.

4. The dosage must be adequate. Martin[11] has emphasized that in the treatment of a tumour extending beneath the surface by external radium therapy the radium-skin distance should be so chosen that the dose at the level of the base of the tumour should be just lethal, the dose at the subcutaneous tissues not sufficient to interfere with the blood supply, and the skin dose one that will produce a lesion that heals readily.

Paterson[14] has established the approximate levels of the tolerance doses in γ *r* units for skin and mucosa in various parts of the body for a total irradiation period of eight days, and also the approximate lethal dose levels for certain types of tumour treated over this period.

Not only must the dosage be adequate in amount, but it must be distributed over an area well wide of the lesion. In the treatment of malignant lesions it is advisable to irradiate an area at least one centimetre beyond the edge of the growth. It may be advisable in those lesions likely to spread to regional glands, to include a much wider area. The experienced radium therapist will judge each case on its merits, and adjust the factors of distance, area and dose accordingly. One may say that, as in the surgical treatment of malignant disease, radium therapy must be radical.

Recently an article has been published dealing with dosage for cylindrical distributions of radium; in it, Paterson[17] draws attention to the inadequacy of the old type of neck pack, in which the radium is arranged at a distance of one or two centimetres on a large Columbia paste mould. The depth dose in this case must be far too low to produce disappearance of deep lesions in the neck, and it is probable that a distance of at least four or five centimetres with a consequently large amount of radium is necessary in the treatment of most conditions in the neck by this method.

By far the greatest advance in radium therapy in the last decade has been on the physical side in putting dosage on a sounder scientific basis. This has resulted in much improved clinical results at the Manchester Radium Institute, particularly in mould work, and a consequently greater use of the method.

There is still, however, need for much research, especially on the clinical side, into irradiation time, intensity and dose, and their interrelations, with respect to various types of malignant disease.

It can be said with Meigs:

> It must be remembered that the use of radium seems notoriously simple to those who know nothing about it, but it is extremely complicated to those who know a great deal.

Summary.

1. An account is given of surface γ therapy by means of specially made moulds and applicators.

2. The wholesale use of unfiltered or lightly filtered plaques is condemned.

3. The methods of construction of various moulds and applicators, especially those in use at the Manchester Radium Institute, are described and the advantages and essentials for success of the methods are discussed.

4. A plea is made for the concentration of radium work at large centres, where the more complicated methods of modern therapy can be undertaken, large amounts of radium (or radon) are available for these methods, active cooperation between the radiotherapist, surgeon and physicist can be obtained, and research into new methods instituted.

Acknowledgement.

I am indebted to Dr. Ralston Paterson for permission to publish an account of the methods at present in use at the Manchester Radium Institute.

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CREATINE RETENTION IN BLOOD AND CEREBRO-SPINAL FLUID.[1]

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CREATINE, or methyl-guanidine-acetic acid, occurs in large amounts in the striped muscles of mammals (0·57% to 0·6%) and to a less amount in smooth muscle (0·09% to 0·15%). In brain tissue it occurs in amounts of 0·1% to 0·16%. Little is known of the creatine content of the blood and cerebro-spinal fluid in health and disease.

A. Hunter, in his monograph on creatine and creatinine,[1] which comprises the literature up to 1927, states that only an approximate idea of the true creatine content of the blood is obtainable; and with all due reserve he accepts four milligrammes *per centum* as the best approximation at present available for the average creatine content of normal human blood. Furthermore, he mentions as generally agreed that creatine is concentrated chiefly in the corpuscles. At that time, creatinine retention in nephritis was well recognized. Little, however, was known about the fate of creatine in the same condition, and Hunter failed to make mention of it. Gavrila, Vior and Ramneantzu,[2] a few years later, in a series of twenty-four chronic nephritics found not only increased creatinine content, but sometimes also increased creatine values, particularly in the terminal stages. Bohn, Friedsam and Hahn[3] obtained creatine values on normal serum which were about one-sixth of those obtained by Gavrila and his collaborators on normal blood. In renal disease these authors observed creatine retention approaching about the same magnitude as creatinine retention. Recently, in acute experimental renal insufficiency produced in dogs, marked creatine retention was noticed which was confined mostly to plasma.[4] The question of the creatine content of blood plasma, cells and cerebro-spinal fluid of human beings, both normal and nephritic, is investigated in the present communication.

[1] From the Gordon Craig Urological Research Laboratory, Department of Surgery, University of Sydney.

Technique.

Filtrates.—Creatinine and creatine determinations were performed on plasma, serum, cells, whole blood, and spinal fluid. Tungstic acid filtrates were prepared by adding to one volume of plasma, cells or blood, three volumes of a solution containing 1·5% anhydrous sodium sulphate and 1·4% sodium tungstate. After this had stood for fifteen minutes, one volume of two-thirds normal sulphuric acid was added in the case of cells and whole blood, and one volume of one-third normal sulphuric acid was added in the case of plasma or serum. In the case of cerebro-spinal fluid, filtrates had only to be prepared in the presence of appreciable amounts of protein.

Determination of Preformed Creatinine.—Creatinine was determined by the method of Folin[5] and also by two modifications of the new dinitrobenzoic acid method.[6][7]

Determination of Creatine.—Creatine present in blood filtrates and spinal fluid was converted into creatinine by acid hydrolysis under pressure. To five cubic centimetres of filtrate was added 0·4 cubic centimetre of 20% hydrochloric acid solution. This was autoclaved at ten pounds' pressure for twenty minutes. The mixture was then neutralized with sodium hydroxide, litmus paper being used as an indicator. After the mixture had been made up to a convenient volume the total creatinine content was determined both by the picric acid method and by the dinitrobenzoic acid methods. The creatine expressed as creatinine was obtained by subtracting the preformed creatinine from the total creatinine.

The Dinitrobenzoic Acid Method for Determination of Creatinine.

Bolliger's Method.[6]—Two cubic centimetres of the neutralized filtrate are transferred to a test tube and 0·4 cubic centimetre of a 10% solution of 3·5 dinitro-sodium benzoate and 0·4 cubic centimetre of normal sodium hydroxide are added. In another test tube 2·0 cubic centimetres of the standard solution are treated in the same manner simultaneously. After the two solutions have been allowed to stand for ten minutes they are compared in a colorimeter. The colour developed is a purplish red. The creatine standard has to agree with the unknown within about 50% in order that a reliable colour comparison may be obtained.

Langley and Evans's Method.[7]—To 10·0 cubic centimetres of tungstic acid filtrate (1:10) in a

test tube and to 0·01 or 0·005 milligramme of creatinine in 10·0 cubic centimetres of solution in another test tube are added 3·0 cubic centimetre portions of saturated sodium dinitro-benzoate and 0·5 cubic centimetre of 10% sodium hydroxide. The tubes are shaken and allowed to stand for ten minutes. Within the following ten-minute interval the solutions are compared in a colorimeter. The readings are referred to a graph, from which the creatinine content of the filtrate is obtained.

In the present paper only five cubic centimetres of a 1:5 filtrate have been used. Accordingly, half the amounts of the reagents have been added and stronger standards have been applied.

Results.

Creatine Content of Cerebro-Spinal Fluid.

Normal Cerebro-Spinal Fluid.—Our specimens were obtained primarily for the Wassermann reaction and during encephalography. All these patients, as far as was known, did not suffer from renal insufficiency. Those suffering from diseases of the central nervous system are considered separately. As shown in Table I, the values for preformed creatinine were found to vary from 0·6 to 0·8 milligramme *per centum*. The values for total creatinine were found to vary from 0·9 to 1·1 milligrammes *per centum*. The values for creatine expressed as creatinine range from 0·2 to 0·4 milligramme *per centum*.

TABLE I.

Creatine and Creatinine Findings in Cerebro-spinal Fluid.

Preformed Creatinine. (Milligrammes *per centum*.)	Total Creatinine.	Creatine Expressed as Creatinine. (Milligrammes *per centum*.)	Diagnosis.
0·7	1·0	0·3	Normal.
0·7	1·0	0·3	Normal.
0·8	1·0	0·2	Normal.
0·6	0·9	0·3	Normal.
0·8	1·1	0·3	Normal.
0·8	1·2	0·4	Normal.
0·6	1·2	0·6	Hydrocephalus.
0·7	1·3	0·6	Mental deficiency.
0·4	1·4	1·0	*Encephalitis lethargica.*
0·4	0·6	0·2	Cerebral tumour.
0·6	1·2	0·6	Hydrocephalus.
1·1	1·3	0·2	Epilepsy
1·1	1·3	0·2	Epilepsy.
1·1	1·7	0·6	General paralysis of the insane.
5·2	7·2	2·0	Chronic interstitial nephritis (blood urea 378).
0·8	1·6	0·8	Malignant hypertension.

Cerebro-Spinal Fluid from Patients with Diseases of the Nervous System and with Renal Insufficiency.—No great deviations from normal were found in such diseases of the nervous system as epilepsy, encephalitis, hydrocephalus and mental deficiency (Table I). On two occasions only, spinal fluid of nephritics came to examination. In the first instance, a case of malignant hypertension, the preformed creatinine was found to be 0·8 milligramme *per centum* and the creatine 0·8 milligramme *per centum*. In the other case, the patient, with chronic interstitial nephritis, which proved fatal two days after the specimen was obtained, showed a preformed creatinine of 5·2 milligrammes *per centum* and a creatine content of 2·0 milligrammes *per centum*.

Cerebro-Spinal Fluid Obtained after Death.—These specimens were obtained by cisternal puncture at varying intervals after death. As shown in Table II, little or no deviation from normal is observed in the preformed creatinine content of these cerebro-spinal fluids. The creatine content, however, is found to rise very sharply after death in patients without or with renal impairment during life. Patients 1 and 2, for example, showed a normal creatinine content six and ten hours after death respectively, while the creatine content in both cases was eleven milligrammes *per centum*. Another specimen of cerebro-spinal fluid from a fatal case of chronic interstitial nephritis (Patient 4), obtained about ten hours after death, also showed a creatine content of eleven milligrammes *per centum*. The preformed creatinine content was seventeen milligrammes *per centum* in this case. In Patient 6 the organs were already in a state of decomposition.

Creatine Content of Plasma, Serum, Cells and Whole Blood.

Patients Not Suffering from Renal Insufficiency.—In a previous communication[6] it was shown that the preformed creatinine content of the blood of normal individuals did not exceed 0·8 milligramme *per centum* when measured by the dinitrobenzoic acid method. In the present investigation (Table III) it was found that the creatinine content might be as high as 1·0 milligramme *per centum* in ambulatory patients not suffering from renal insufficiency. The creatinine content of cells and plasma is about

TABLE II.

Creatine and Creatinine Findings in Cerebro-Spinal Fluid Obtained Post Mortem.

	Preformed Creatinine. (Milligrammes *per centum*.)	Total Creatinine. (Milligrammes *per centum*.)	Creatinine Expressed as Creatine. (Milligrammes *per centum*.)	Hours After Death.	Age in Years.	Cause of Death.
1	0·8	12·5	11·7	6½	64	Intestinal obstruction.
2	0·6	12·0	11·4	12	59	Carcinoma of bronchus.
3	1·0	11·0	10·0	3½	80	Congestive cardiac failure.
4	17·0	28·0	11·0	12	26	Chronic nephritis.
5	3·3	20·9	16·7	16	60	Cerebral haemorrhage.
6	2·0	23·0	21·0	10	23	Septicæmia.

equal. The creatine content, however, of plasma and serum does not exceed 0·3 milligramme *per centum* according to the dinitrobenzoic acid method. If the serum is allowed to stand with the clot for twenty-four hours or more, the values are found to be from 50% to 100% higher. The creatine content of the cells is very much higher than that of the plasma, that is, 2·6 to 4·2 milligrammes *per centum* (Table III). Folin's method gives lower creatine values for cells, because the preformed creatinine is found to be higher by this method.

TABLE III.

Creatine and Creatinine Findings in Normal Human Blood.

Number.	Preformed Creatinine. (Milligrammes per centum.)		Total Creatinine. (Milligrammes per centum.)		Creatine Expressed as Creatinine. (Milligrammes per centum.)		Material.
	D.[1]	F.	D.	F.	D.	F.	
1	0·6	1·2	2·6	3·0	2·0	1·8	Whole blood.
2	0·6	1·6	3·6	3·4	3·0	1·8	Whole blood.
3	0·7		3·1		2·4		Whole blood.
4	0·8	1·0	1·1	1·2	0·3	0·2	Serum.
5	1·0		1·3		0·3		Plasma.
	0·8		5·0		4·2		Cells.
6	0·7		1·0		0·3		Plasma.
	0·7		4·9		4·2		Cells.
7	0·9		1·2		0·3		Plasma.
	1·0		3·6		2·6		Cells.

[1] D = Dinitrobenzoic acid method. F = Folin's method.

Patients Suffering from Renal Insufficiency.—In nephritic patients the creatine content of the plasma was found to be increased from 0·3 to 9·0 milligrammes *per centum* (Table IV). In Patient 3 twelve hours after death the plasma creatine content was 31 milligrammes *per centum*, an increase of 26 milligrammes *per centum* compared with the specimen obtained shortly before death. This is in contrast to the small increase in creatinine over the same period of time.

The creatine content of cells was found to vary from 3·0 to 7·2 milligrammes *per centum*. Changes of approximately similar magnitude were observed for whole blood.

Discussion.

Technique.

In addition to the classical Jaffé reaction for the detection and determination of creatinine as applied to blood filtrates by Folin,[5] the determination of creatinine by means of dinitrobenzoic acid has recently been described. This method has been applied to blood filtrates in three modifications, namely, those by Benedict and Behre,[8] by Bolliger[6] and by Langley and Evans.[7] The methods used by Benedict and Behre and by Bolliger differ, inasmuch as the former uses as reagent an alcoholic solution of dinitrobenzoic acid, while the latter uses an aqueous solution of sodium dinitrobenzoate. These two methods give essentially the same results and suffer from the drawback that normal amounts of creatinine in a 1:10 filtrate

TABLE IV.

Creatine and Creatinine Findings in the Blood of Patients Suffering from Renal Insufficiency.

Number.	Preformed Creatinine. (Milligrammes per centum.)			Total Creatinine. (Milligrammes per centum.)			Creatine Expressed as Creatinine. (Milligrammes per centum.)			Material.	Diagnosis.	Date.	Blood Urea. (Milligrammes per centum.)
	D.	L.E.	F.	D.	L.E.	F.	D.	L.E.	F.				
1	16·5	—	18·7	21·4	—	21·0	4·9	—	2·3	Blood.	Pyonephrosis.		
2	4·3	—	—	7·2	—	—	2·9	—	—	Blood.	Renal tuberculosis.		160
3	21·1	—	—	28·8	—	—	7·7	—	—	Plasma.			
	20·4	—	—	27·6	—	—	7·2	—	—	Cells.	Chronic nephritis.	6/5/37	316
	21·5	—	—	26·4	—	—	4·9	—	—	Blood.			
	20·4	—	—	28·8	—	—	8·4	—	—	Plasma.[1]			
	20·4	—	—	29·4	—	—	9·0	—	—	Plasma.[2]		18/5/37	
	19·6	—	—	27·4	—	—	7·8	—	—	Blood.			
	36·5	—	—	41·8	—	—	5·3	—	—	Plasma.[3]		1/6/37	
	39·0	—	—	70·0	—	—	31·0	—	—	Plasma.[4]		2/6/37	
4	5·0	—	—	6·2	—	—	1·2	—	—	Plasma.	Chronic nephritis.	9/6/37	164
	5·0	—	—	8·1	—	—	3·1	—	—	Cells.			
	6·6	—	—	7·4	—	—	0·8	—	—	Plasma.		30/6/37	
	6·5	—	—	9·5	—	—	3·0	—	—	Cells.			
	8·6	—	8·8	8·9	—	9·4	0·3	—	0·6	Plasma.		26/7/37	
	8·8	—	8·5	10·7	—	11·3	1·9	—	2·8	Cells.			
5	8·3	—	—	8·8	—	—	0·5	—	—	Plasma.	Carcinoma of the bladder.		
	7·0	—	—	10·2	—	—	3·2	—	—	Cells.			
6	6·0	—	5·3	6·3	—	5·6	0·3	—	0·3	Plasma.	Chronic nephritis.		200
	6·9	—	—	11·6	—	11·6	4·7	—	—	Cells.			
7	2·4	—	—	3·8	—	—	1·4	—	—	Plasma.	Hypertrophied prostate.		90
	2·6	—	—	8·1	—	—	5·5	—	—	Cells.			
8	—	2·7	2·7	—	2·8	2·9	—	0·1	0·2	Plasma.	Hypertrophied prostate.		74
	—	2·3	—	—	8·9	8·1	—	6·6	—	Cells.			
9	—	2·4	2·3	—	2·5	2·6	—	0·1	0·3	Plasma.	Hypertrophied prostate.		
	—	2·4	—	—	7·6	7·6	—	5·2	—	Cells.			
10	—	1·6	2·3	—	2·4	2·5	—	0·8	0·2	Plasma.	Urethral stricture.		
	—	2·4	—	—	6·7	6·5	—	4·3	—	Cells.			
11	7·7	8·0	8·3	7·9	8·3	9·4	0·2	0·3	1·1	Serum.[5]	Chronic nephritis.		161
	6·3	—	6·3	7·9	—	7·6	1·6	—	1·3	Serum.[6]			
12	2·8	—	3·0	2·8	—	3·2	0·0	—	0·2	Serum.	Chronic nephritis.		
13	—	—	1·5	—	3·2	3·5	—	—	2·0	Serum.	Hypertrophied prostate.		43
14	—	—	1·4	—	2·7	2·4	—	—	1·0	Serum.	Hypertrophied prostate.		37
15	—	—	1·0	—	2·3	2·0	—	—	1·0	Serum.	Hypertrophied prostate.		35

D. = Dinitrobenzoic acid method (Bolliger). L.E. = Langley and Evans's method. F. = Folin's method.

[1] Filtrate autoclaved at 10 pounds pressure for 20 minutes.
[2] Filtrate heated at 100° C. for two hours.
[3] Plasma obtained the day before death.
[4] Plasma obtained twelve hours after death.
[5] Determination executed four hours after venepuncture.
[6] Same serum determination executed thirty hours after venepuncture.

cannot be determined. Langley and Evans use as reagent dinitrobenzoic acid dissolved in a slight excess of sodium carbonate. This apparently minor modification has some distinct influence on the production of the colour. Smaller concentrations of creatinine, that is, less than 0·1 milligramme *per centum* in the filtrate, still give a readable colour. However, with elevated creatinine values as found in patients with creatinine retention, the values obtained by the three modifications of the dinitrobenzoic acid methods are about equal and agree closely with those obtained by Folin's method.

For the hydrolysis of creatine autoclaving at a temperature of 120° C. was employed, and no material difference could be observed between blood filtrates treated at this or at a lower temperature for a longer period. Again, the three methods show fair agreement, which may be considered as evidence in favour of the assumption that the additional chromogenic material in the blood, as observed after acid hydrolysis, represents creatine, at least in those cases in which about more than half a milligramme of chromogenic material can be discovered.

Cerebro-Spinal Fluid.—Creatinine is always found to be present in apparently normal cerebro-spinal fluid in amounts comparable with those present in blood, plasma and cells, when measured with the dinitrobenzoic acid method. Creatine, on the other hand, is present to such a slight extent that sometimes one may doubt its presence in normal cerebro-spinal fluid. This is in distinct contrast to the findings of Gavrila,[9] the only worker who previously investigated cerebro-spinal fluids. His results, obtained from normal subjects and by using Folin's method, vary from 3·2 to 5·09 milligrammes *per centum*, and they closely approximate his findings in whole blood. In nephritics his values varied from 3·3 to 7·0 milligrammes *per centum*.

Plasma and Cells.—The creatine content of the plasma of human beings was found to be approximately the same as that of cerebro-spinal fluid, that is, 0·2% to 0·4%, and about ten times as much is found to be present in cells. In nephritic patients the maximum increase of creatine as measured in plasma was 9·0 milligrammes *per centum* (Table IV, Case 3). This and similar figures (Table IV) are not impressive if they are compared with the figures obtained for preformed creatinine. Actually, however, they represent an approximately equal percentage increase if they are compared with the amounts of creatinine and creatine found in normal plasma.

The increase in the creatine content of the cells of nephritic patients is even less impressive than that in the case of plasma, if the normal creatine content of cells is considered to be 2·6 to 4·2 milligrammes *per centum*.

The comparatively small alterations of the creatine content of the plasma of nephritic patients are in marked contrast to the findings in a series of anuric dogs. On that occasion it was found that the creatine content of the plasma was distinctly increased as compared with that of the cells.[4] This difference is noted in the two species, human and canine, and may have some bearing on the cause and duration of "surgical uræmia" as observed in man and in the dog. In the dog uræmia following complete urinary obstruction usually becomes fatal in four to five days. Human beings survive bilateral acute obstruction for about twelve days.

These findings with regard to creatine retention as observed in man and in dogs call to mind the relative potassium retention in the two species, which is somewhat parallel to that of creatine. In human beings, both constituents, creatine and potassium, are usually increased to a comparatively small degree in terminal nephritis or urinary obstruction. In dogs, potassium and creatine are greatly increased under similar conditions.[10]

Finally, we call attention to the *post mortem* rise in creatine as observed in cerebro-spinal fluid and in the plasma of human beings (Tables II and IV, Case III). Since a pronounced *post mortem* rise has been reported with regard to potassium, one might speculate on some relationship between potassium and creatine in connexion with *post mortem* changes.

Summary.

The creatine content of cerebro-spinal fluid, plasma, cells and whole blood has been examined. In normal individuals it was found to vary from 0·2 to 0·4 milligrammes *per centum* in cerebro-spinal fluid and plasma. In cells it was found to vary from 2·6 to 4·2 milligrammes *per centum*. Specimens of cerebro-spinal fluid obtained *post mortem* exhibit a sharp rise in creatine content.

Creatine retention occurs in cerebro-spinal fluid, in plasma and in cells of nephritic individuals, but not to an extent which would warrant its estimation for diagnostic and prognostic purposes in preference to creatinine determinations.

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STRANGULATED HERNIA.[1]

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STRANGULATED hernia is a condition which, like the poor, is always with us—in fact, it has shown a tendency to increase in recent years. It is well that the subject should be discussed at intervals so that in our stock-taking we may note what measure of success has attended our efforts. Perhaps one may remark that this subject is much overdue for discussion. In 1932 the subject of acute intestinal obstruction was fully covered at the centenary meeting of the British Medical Association in London, yet strangely enough its most important cause, strangulated hernia, was not discussed. Sir Henry Newland[1] at this centenary meeting remarked: "It is to the surgeons attached to the medical schools throughout the Empire that the profession looks for light and leading." And so it is right that surgeons should inquire whether this condition, strangulated hernia, is being satisfactorily treated, but, as my figures will show, a mortality of approximately 20% is not one which any of us can regard with complacency.

Have we improved our treatment in recent years? I doubt it very much. C. L. Gibson,[2] in an excellent article published in 1900, gives the following results: strangulated hernia with gangrenous gut, 354 cases with 120 deaths, a mortality of 34%; treated by means of resection and primary anastomosis, 226 patients with 58 deaths, a mortality of 26%; treated by means of resection and primary anastomosis by Murphy's button, 63 patients with 14 deaths, a mortality of 22%.

It is extremely doubtful whether these results can be bettered at the present day, when we remember that they are all cases of gangrenous hernia. For comparison I can give the figures for the treatment of all patients with strangulated hernia (inguinal and femoral only) at the Dunedin Public Hospital for the past twenty-two years, from 1915 to 1936 inclusive: there were 121 cases with 24 deaths, a mortality of 19·8%. (There were an additional nine cases in which reduction occurred just before operation, or on the operating table itself, but these are not included.) If we consider the gangrenous cases, which were fourteen in number, the results are as follows: eight patients were treated by means of resection and primary anastomosis, of whom five died; five patients were treated by exteriorization only, of whom five died; and in one case the hernia was put back into the abdomen owing to the patient's collapse, this patient dying. This makes a total of fourteen cases with eleven deaths. Moreover, it is not only the gangrenous cases which are the cause of the high mortality. Peritonitis, shock (sometimes due to spinal anæsthesia) and pulmonary complications all claim their victims, and these deaths (ten in number) nearly equal those due to actual gangrene of the gut.

[1] Read at the fifth session of the Australasian Medical Congress (British Medical Association), August, 1937.

All is clearly not well with our present methods, and I would therefore venture some suggestions. In the first place I wish to make a plea for clearer and better guidance from the standard text-books on surgery.

For example, the usual treatment advised for the case in which the gut is of doubtful viability is to bring the loop out, to wash it with saline solution, and to pass a rod through the mesentery or to fix the loop at the neck of the sac with sutures.[3] This treatment, when carried out at our hospital, was followed by a 100% mortality. The wound cannot fail to become infected whether the bowel gives way or not; and also, owing to the normal sphincter action of the inguinal canal, the condition of intestinal obstruction is not adequately relieved. The normal tone of the external oblique and of the other flat muscles of the abdomen tends firmly to close and compress the lumen of any bowel which is brought out through the inguinal region. If an enterostomy is planned, even a muscle-splitting incision in the right or left iliac fossa is not so favourable as in the median subumbilical incision, for with the former incision there is a similar compressing effect upon the bowel. In a series of cases of exteriorization of doubtful bowel reported by Morris and Johnston[4] this year, six out of seven patients died, a mortality of 85·7%. I would suggest that this method of treatment, that is, exteriorization of doubtful gut, is unwise, and should not be recommended. The usual attempts should be made to improve the circulation in the affected bowel by hot towels and adequate waiting, and if these measures are successful the loop can be returned to the peritoneal cavity. If the application of hot towels is unsuccessful, the affected loop should be brought out through a short mid-line subumbilical incision, the unhealthy gut should be cut off, and a catheter should be tied into each open end. I suggest that the leaving of a loop of doubtful gut in the wound is dangerous treatment and should be given up.

There is no need to hurry the process of warming by hot towels the dark-coloured intestine, for the duration of the operation is quite immaterial: a long operation under local anæsthesia does not produce shock.

Truscott,[5] in Dean Lewis's "Practice of Surgery" (1935), has well stated the position when he says:

> It may take some time to reach a conclusion while the behaviour of the questionable gut is being closely watched. Clearly there is a great advantage in working under local anæsthesia, which permits all the time desired for this purpose without adding to the patient's burden or hurrying the surgeon's decision, as is unavoidably the case with general anæsthesia.

Elman[6] has produced evidence that a sudden relief of the obstructed portion of bowel is dangerous, and he advises interrupted release of its contents, that is, a slow decompression of 100 cubic centimetres every thirty minutes. This appears to be a wise procedure and should lessen shock, which is sometimes a grave problem. Knight and

Slome[7] have done some painstaking research at the Experimental Research Department of the Royal College of Surgeons of England, and their efforts to find an explanation of death in animals suffering from strangulated hernia have advanced our knowledge, though they have not yet been able to identify the actual toxic substance produced in the wall of the damaged bowel.

In cases in which the gut is gangrenous and the patient is in good condition, the orthodox treatment is resection and immediate anastomosis. The mortality in the Dunedin Hospital series is 62·5%, and the average mortality in most hospitals approximates to 50%. The advantage of immediate resection is obvious, but the occasions for its employment are really very few indeed. In the occasional case in which resection and immediate anastomosis are to be performed, it seems to be doubtful wisdom to do it through the neck of the sac. It would appear preferable to bring out the bowel through a mid-line incision and to do the anastomosis in comfort. In the ordinary case it is always difficult to get the bowel sufficiently free to allow a good loop to be brought down, and it is certain that for a satisfactory and safe anastomosis a free removal of the proximal loop is essential. This cannot generally be done in operations through the inguinal canal.

Wangensteen[8] has shown the excellent results that follow the use of the intranasal suction duodenal catheter in the treatment of patients with intestinal obstruction, and this method should be employed as a routine measure after resection of the bowel. It will probably obviate the necessity for an enterostomy, as it produces the same effect, but in a perfectly safe manner. His method should be studied and made use of, as it represents a contribution of real value in the handling of these patients.

In the vast majority of cases in which the bowel is irreparably damaged, there is no doubt but that the simpler operation, that is, a median subumbilical gun-barrel enterostomy, with complete removal of the gangrenous loop, will usually be the best treatment. However, in children an anastomosis is generally to be preferred to an enterostomy. The tying-in of a catheter in each opening and a slow decompression of the proximal obstructed gut aids in minimizing shock and in keeping the wound free from contamination for the first few days. Much consideration is needed in the post-operative care of these patients: morphine should be given as required, saline solution should be administered up to physiological tolerance, blood transfusion should be given when indicated, and nothing should be given by mouth except when suction drainage of the duodenum by nasal tube as advocated by Wangensteen is employed, when fluids by mouth are permissible.

When the bowel is gangrenous and the patient is in poor condition, the making of an artificial anus in the inguinal region is usually advised in the standard text-books. As already stated in the first paragraph, this is probably not the best treatment for such a patient. The wound becomes grossly infected, the artificial anus does not drain, and so the operation is most unsatisfactory. I submit that it would be better to give up this form of treatment and to perform a median subumbilical gun-barrel enterostomy with a catheter tied into each limb of the enterostomy. At a later stage, which should not be too long deferred, a further operation will be required to reconstitute the intestinal pathway.

Anæsthesia.

The majority of the patients at Dunedin Hospital were operated on under general anæsthesia, ether preceded by ethyl chloride being used. It is noted that ten operations were performed under local anæsthesia alone, with nine recoveries. In three additional cases local anæsthesia was used as the main anæsthetic agent, but a very little inhalation anæsthetic was used at one stage. There were three recoveries, one of these being a patient who had had a resection with immediate anastomosis. If we add these three cases to the ten previously mentioned we have thirteen cases with twelve recoveries, a mortality of 8·4% for patients operated on (mainly) under local anæsthesia.

Wood Power,[9] in a masterly article in *The British Medical Journal* (1934), strongly advocates the use of local anæsthesia as giving a much lower mortality than either spinal or inhalation anæsthesia. In a series of thirty-four consecutive cases in which operation was performed under local anæsthesia he had three deaths, a mortality of 8·82%. Harvey Cushing,[10] in a good article in *Annals of Surgery* (1900), made a plea for the employment of local anæsthesia for these patients, who are often serious risks apart from their strangulation obstruction.

I would ask, why is it so difficult to persuade surgeons to employ this shockless method of operating in these dangerous cases of strangulated hernia? Perhaps the reason is that surgeons do not choose a method which necessitates attention to both ends of the patient at the same time—I refer to the psychical calming of the patient during the operation. Fortunately a method of premedication has been devised by a well-known Australian surgeon, C. E. Corlette, of Sydney, which consists of step-by-step doses of morphine and hyoscine, and this entirely removes the worry of having to look after the patient's mental state during operation. The patient sleeps or dozes throughout the operation in most cases, or if he does not do this, he is at any rate quiet and comfortable, needing no particular attention. A further important advantage of morphine-hyoscine premedication is that the likelihood of shock following the release of bowel strangulation is thereby greatly reduced by the protection thus afforded the higher cerebral centres. It has always seemed strange to me that surgeons do not invariably choose local anæsthesia for all cases of strangulated hernia. Operation can be carried out satisfactorily and shocklessly, including the intestinal anastomosis or

enterostomy. Even in children local anæsthesia should be used, but if desired a little ether also is permissible, since actual gangrene of the bowel in children is exceedingly rare. Practice is undoubtedly needed if the surgeon is to be successful, and this must be obtained by operating on patients with ordinary inguinal and femoral hernia under local infiltration anæsthesia. Yet this priceless opportunity is all too seldom seized, and until this is done by all surgeons no further reduction is likely in the present high mortality of strangulated hernia.

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(7) G. C. Knight and D. Slome: "Intestinal Strangulation", *The British Journal of Surgery*, Volume XXIII, 1936, page 820.
(8) O. H. Wangensteen: "Therapeutic Considerations in the Management of Acute Intestinal Obstruction: Technic of Enterostomy and Further Account of Decompression by Employment of Suction Siphonage by Nasal Catheter", *Archives of Surgery*, Volume XXVI, June, 1933, page 933.
(9) R. W. Power: "Strangulated Hernia: Its Prevention and Treatment under Local and Other Anæsthetics", *The British Medical Journal*, Volume I, May 5, 1934, page 787.
(10) H. Cushing: *Annals of Surgery*, Volume XXXI, 1900, page 1.

Reviews.

PRACTICAL ANATOMY.

THE question is frequently asked: "Need dissecting manuals be so large?" The "Manual of Practical Anatomy", by Frazer and Robbins,[1] supplies an answer in the negative. These authors have succeeded in delivering the necessary account within two volumes of less than one thousand pages in all, with, as far as can be seen, no omission of importance. The reduction is effected by the relegation of all superfluous matter (X ray plates *et cetera*) to their rightful place, the larger text-books of anatomy, where the student can consult them at his leisure, and by an admirable deletion of all redundancy from the text.

The name of J. E. Frazer on the title page of any book on human anatomy is a guarantee of the accuracy and intellectual integrity of the contents; at the same time it promises a novel mode of attack. It is no disparagement of the junior author to emphasize the name of Frazer, for these two volumes breathe the spirit which has made the school at Saint Mary's Hospital one of the great centres for the teaching of human anatomy.

The most striking feature of this book is the liberality with which it is illustrated: in less than one thousand pages of text there are nearly six hundred figures—an extraordinary proportion. And in place of the usual bald catalogue of facts there is a distinct effort on the part of the authors to teach anatomy. To this end they take frequent excursions into morphological, embryological and histological fields, make free use of explanatory thumbnail sketches and diagrammatic cross-sections and even indulge in occasional appeals to functional purpose. Thus the reader experiences the comforting feeling that a personal interest is being taken in his anatomical education and that he is learning the "how" and "why" of the human body. In this connexion, too, must be mentioned the useful glossary of terms at the end of each volume, for it is no exaggeration to state that if a student knows what the name of a structure means he has considerably less difficulty in assigning that structure to its correct place. The order of dissection is readily adapted to the requirements of any course.

Some readily corrected faults demand attention. In the text compression has occasionally been carried to the stage of obscurity. In addition, the terminology is by no means uniform. B.R. terms are always given, but often alternatives from the B.N.A. or O.T. are employed with little qualification. While it is true, as the authors state, that the older terms are more familiar, to the beginner no terminology is familiar, and if he is confronted with several alternative names for a single structure at the outset of his career only confusion can result. It is useful to mention the older names, but they should be given emphasis secondary to that placed on the titles which it should be the purpose of the book to teach. The illustrations are not all of uniform quality. The majority, and especially the explanatory diagrams, are excellent, but in many greater clarity would result if the outlines of the major structures were rendered more boldly. Many of the figures are coloured, but not always with happy results. The colours frequently produce obscurity, especially when, as often happens, they are not accurately superimposed on the structures to which they belong. The worst offenders in this respect are the figures borrowed from other authors. Many of the coloured figures would be better rendered plain; on the other hand, some of the plain diagrams would benefit from the judicious introduction of a little colour. Also, there is much unnecessary repetition of some of the figures—one appearing no less than three times within the space of fifty pages.

The volumes are adequately bound, but it is a matter for comment that publishers of practical manuals do not take advantage of the excellent washable bindings now available.

Clarification of the text, the introduction of greater uniformity in nomenclature and a revision of the figures in the editions which are certain to follow will make this a serious rival to the older, well-established manuals. The aim and scope of the book are worthy of the highest praise, and teachers seeking a change from the usual routine will turn gladly to the escape which it offers.

[1] "Manual of Practical Anatomy", by J. E. Frazer, D.Sc., F.R.C.S., and R. H. Robbins, M.A., M.D. Volume I: Upper Limb, Lower Limb and Abdomen; pp. 546, with illustrations. Volume II: Thorax, Head and Neck, Central Nervous System, Eye and Ear; pp. 463, with illustrations. 1937. London: Baillière, Tindall and Cox. Large crown 8vo. Price: 10s. 6d. net, each volume.

ORTHOPTICS AND SQUINT.

MUCH has been written recently on "Practical Orthoptics in the Treatment of Squint", but nothing will prove of greater value to oculists and other orthoptic workers than the book bearing this title written by Dr. Keith Lyle and Miss Sylvia Jackson.[1] The association of this ophthalmic surgeon and the senior orthoptist at the Royal Westminster Ophthalmic Hospital, London, has resulted in broader views of, and deeper insight into, the many problems that arise in the treatment of squint. These results prove beyond doubt that such an association of doctor and specially trained lay worker is the ideal combination for the thorough treatment of this deformity.

It is eighteen years since this work was first carried out in a thorough and extensive manner by Miss M. C. Maddox with mechanical devices that utilized electric illumination. Much has been learned since then that is of great assistance to those now attempting this work. Orthoptic work in the future can be carried out most successfully by those who, with special gifts in the control and education of children, have received adequate train-

[1] "Practical Orthoptics in the Treatment of Squint", by K. Lyle, M.A., M.D., M.Chir., M.R.C.P., F.R.C.S., and S. Jackson, with a foreword by C. L. Gimblett, M.A., M.D., M.R.C.P., F.R.C.S.; 1937. London: H. K. Lewis and Company Limited. Demy 8vo, pp. 228, with illustrations. Price: 12s. 6d. net.

ing from oculist and orthoptic worker and who carry out their work under the direct supervision of the oculist in charge of the patients. "Only too often have cases been seen who have received treatment from unqualified persons where definite harm has been done (by stimulation of the false fixation *et cetera*). To protect patients an Orthoptic Board has been formed regulating the training and qualification of orthoptists . . . Before being presented with their diploma, candidates sign an undertaking to treat only cases referred to them by ophthalmologists . . . Orthoptists must possess patience, tact and sympathy; an orthoptist who obtains the best results is one who has teaching ability."

After describing the formation and management of an orthoptic clinic, the authors discuss and illustrate the various instruments that may be used.

The authors' summary of the treatment of the various types of concomitant squint is on sound lines. The analyses of the results obtained by training alone and by training in addition to operation are of great interest. Good results were obtained in 79% of patients in two groups that one would hardly expect to provide equal results, namely, those with normal projection who were trained and operated on, and those with abnormal projection who developed normal projection before operation. These results are particularly good when we realize that training did not commence till after the eleventh year in almost 50% of the cases. The results were only half as good when abnormal projection was not corrected before operation. In this series projection became normal after operation in thirteen of fifteen cases after not more than forty treatments, and single binocular vision was obtained in six of these. It is not proved yet that abnormal projection can lead to a recurrence of a convergence; such results are usually due to faulty operative technique; but it is definitely worth while attempting to obtain normal projection before operation, for it is easier then for the patient rapidly to develop fusion that will correct the common small post-operative squint. Ten of the fifteen patients who developed normal projection before operation did so with less than twenty treatments.

The authors' view that false projection is an endeavour to obtain a degree of fusion is less likely to be correct than that it is simply an accommodation due to recognition of a faulty ocular position. This recognition depends on proprioceptive impulses and the degree of binocular projection established prior to the development of the squint.

The section in the book dealing with the mixed types of squint, namely, those that are associated with a varying degree of paresis of one muscle, or of over-action of its synergist, are particularly good.

All oculists will be interested and possibly their patients benefited by a study of the methods of and the results obtained from the orthoptic treatment of those heterophorias that produce asthenopia. In conclusion, we may add that no oculist can afford to be without this up-to-date concise report from two people who know their subject.

CANCER AND DIET.

IN our efforts to ascertain the exact nature of the cancerous process and the various predisposing factors that may be responsible for its development, no reasonable avenue of inquiry should be neglected. In this connexion, as might be expected, much attention has been given by many workers and writers to the possible rôle that the food we take may play in the genesis of malignant growths. Dr. Frederick L. Hoffman, in "Cancer and Diet", a volume of nearly 800 pages,[1] has with prodigious energy summarized much of the information on this subject already available and has analysed carefully the answers to a lengthy *questionnaire* dealing with persons suffering from cancer and for comparison those free (as yet) from such disease.

Before indicating the scope of this work, it may be as well to point out that we are still uncertain as to whether cancer is a general condition, though manifesting itself locally, or whether, as many believe, it is purely local in origin. If the former is true, then diet may possibly play some rôle in the genesis of cancer anywhere in the body; if the latter, one would expect its effect to be confined to malignant growths of the alimentary canal.

Part I of this work deals with dietary theories of cancer from the earliest times up to 1935 and occupies 117 pages. From an historical point of view the references are of interest, though they cannot be considered of much value until recent years are reached. Nearly two hundred authorities are quoted, but one cannot say that any appreciable light is thrown thereby on the influence of diet on malignant growths.

Part II considers the modern diet in all possible aspects as bearing on the subject. In his summary, Dr. Hoffman points out that the decided increase in the cancer death rate has been accompanied by profound changes in the dietary habits of the world at large, with the substitution to a great extent of modified food products for those consumed in their natural state.

Cancer metabolism, constituting the 240 pages of Part III, contains quotations and discussions on the parts that may be played in the genesis of cancer by alterations in the basal metabolism and intake of calories; by alkalosis and acidosis; by enzymes and hormones; by vitamins; by protein, carbohydrate and fat metabolism; by fluid metabolism, including that of milk, tea, coffee or alcohol; and by mineral metabolism embracing sodium, potassium, magnesium, arsenic, aluminium, manganese, iodine, fluorine *et cetera*.

Part IV, entitled "Dietary Facts Concerning Cancer Patients", consists of an analysis of the answers to some ninety items in a *questionnaire* dealing amongst other matters with food consumed by 2,234 cancer patients and 1,149 non-cancerous controls. This information was collected in the United States of America by assistants who received written instructions concerning the interpretation of the questions. The *questionnaire* and the instructions appear in the appendix. Amongst the separate items which have been analysed and compared may be mentioned: the marital condition of cancer patients and controls, the height and weight, amount of perspiration, vegetarianism, food faddists, smoking, water intake, use of intoxicants, eating between meals, eating meals very hot, use of canned foods, use of purgatives, previous occurrence of appendicitis and gall-stones *et cetera*, and blood pressure. Then comes a consideration of forty-four food products which had been consumed by the cancer patients and the controls, the replies indicating whether none, little, much or very much of each had been eaten.

Dr. Hoffman, in his conclusions, considers that "without a seriously disturbed derangement of the metabolism the local irritation would be wholly ineffective in producing malignant proliferation of the body cells". He is convinced as a result of his study that "the underlying cause of cancer is to be found in an excessive intake of foods of a high organic or mineral content, or generally of an alkaline base instead of acid", and that it is not so much a question of any particular type of food product taken in excess as of food products in general.

One cannot here enter into a detailed criticism of the subject matter of Dr. Hoffman's work. The book provides a wealth of information on the subjects indicated above. The quotations from authors are many, probably too many, and of very unequal value. The reader, however, must judge for himself. A criticism which may legitimately be made on the controls is that we have no means of learning how many of these will eventually themselves suffer from malignant growths and so should be included in the cancer cases. We consider Dr. Hoffman's "Cancer and Diet" a contribution to the study of this disease and a work that contains a mine of information. His analyses present many items of considerable interest and open up aspects that will repay further investigation.

[1] "Cancer and Diet, with Facts and Observations on Related Subjects", by F. L. Hoffman, LL.D.; 1937. Baltimore: The Williams and Wilkins Company; London: Baillière, Tindall and Cox. Medium 8vo, pp. 788, with illustrations. Price: 22s. 6d. net.

The Medical Journal of Australia

SATURDAY, JANUARY 8, 1938.

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UROLOGY AS A SPECIALTY.

THE October, 1937, issue of *The American Journal of Surgery* consists almost entirely of a symposium on urology edited by Hugh Cabot. The first article is an editorial from the pen of Cabot, in which he makes some pertinent observations on specialization in medicine and on urology, or, as he prefers to call it, genito-urinary surgery. Though it is probably to be included among the so-called minor specialties, urology is a most important branch of surgery, a fact that will quickly be realized by a practitioner foolish enough to essay one of its more difficult procedures if he is lacking in either technical skill or clinical judgement. Urology is differently regarded in various parts of Australia. One group of urologists style themselves "pure" urologists, an unfortunate term, for it implies that others are not so pure; we have always understood, however, that the reference is to restriction or type of practice and not to moral character. In other words, urology in some places is almost entirely in the hands of those who limit their practice to that specialty, and in other centres general surgeons still regard it as their province.

Cabot recognizes that the medical profession in America is a "hierarchy" at the head of which is, or should be, the general practitioner. The general practitioner is supported by the physician and surgeon and then come the "almost bewildering group of specialists". He does not think that the subdivision of medicine into specialties is yet complete; but at the same time he points out that though progress is likely to be achieved by this subdivision, it is not without its dangers. The first danger is that contraction of the field may also contract the field of vision. Cabot finds that there has been constant friction between the retreating general practitioner and the advancing horde of specialists; this has not been productive of good and has "shed more heat than light on the subject". He pleads for strengthening of the "hierarchy" and better articulation between its various parts. The other danger of specialization seen by Cabot, and one not often recognized, is the effect of specialization, especially in the narrower fields, on the character of the specialist. To pay attention to a special field throughout life cannot fail to have an unfavourable reaction on the individual—he becomes cramped by his environment and may be crushed by it. The men who will guide the future of medicine will, in Cabot's opinion, not rarely be found among the group of those who have mastered some field in their earlier years, who have felt the compression of their environment, and who have gone on from the mastery of their narrow field to a comprehension of a much larger whole.

There is, of course, a great deal of truth in these statements made by Cabot; they may be applied with advantage, as he applies them in part, to urology. Efficiency as a urologist implies something more than dexterity with the cystoscope; it also calls for more than soundness of judgement and ability to perform surgical operations. Diagnosis in urology is more important than in general surgery—the urologist cannot emulate the general

surgeon who not infrequently performs exploratory laparotomy when the diagnosis is not clear. The general surgeon who undertakes urological practice may not be skilled in diagnostic procedures and disaster may befall him. Equally disastrous may be the surgical adventures of the inadequately trained urological diagnostician. Training in urology should follow an apprenticeship served both in medical and in general surgical wards; otherwise distorted vision will result and disaster will follow. Only in this way will it be possible to avoid the confusion recognized by Cabot "among the group now loosely referred to as urologists". Even when the urologist is adequately trained and has become expert in his specialty, he should include in his reading an account of work done outside it. He will thus preserve a normal balance and be the more likely to add something to the sum of scientific knowledge.

Current Comment.

THE ACTION OF THE DIAPHRAGM IN COUGH.

SOME years ago an editorial comment in a leading medical journal on the subject of the part played by the diaphragm during the act of coughing stated that "in all acts of expulsion . . . the diaphragm adds force to the expulsive effort". Those who can sympathize with the great difficulties experienced by the editorial staff of a technical journal in serving the cause of accuracy will feel for the editor when he was asked by a correspondent how the musculature of the diaphragm could act in this way, and still more when he had in honesty to reply that there was no available evidence that the diaphragm added power to any expulsive expiratory acts. This is not a comment on medical editors; it is merely an illustration of how obscure an apparently simple physiological problem may be in reality, and some proof of the problem thus stated is given by Pol Coryllos in an account of some original work he has carried out.[1] This writer is well known for his practical contributions to the clinical physiology of the lungs; and he points out that since operations on the phrenic nerve have become common for various pulmonary complaints, it is essential that we should know all we can about the functions of the diaphragmatic muscle thus put out of action. Cough is, in the oft-quoted and apt phrase of Jackson, the "watchdog of the lungs". When we paralyse one half of the diaphragm do we make the act of coughing more or less difficult? Opinion has been divided. H. F. Wilson, in a paper published in this journal and quoted by Coryllos, found no constant change as regards cough in pulmonary tuberculosis and bronchiectasis after phrenic evulsion. Others have regarded the diaphragmatic paralysis as a positive advantage in this regard, making expectoration easier; others again see in it a sinister danger, owing to a damming back of the secretions of the lung. Coryllos has attacked the problem in the correct way, setting out to investigate experimentally the mechanics of cough. He points out that the diaphragm is supposed to be a purely inspiratory muscle; if this is so, it should have no influence upon a purely expiratory act. But is cough a purely expiratory act? This question epitomizes his inquiry, and he has now come to the conclusion that cough is not strictly and solely an expiratory act. The material for his experiments was found in patients who were undergoing treatment by artificial pneumothorax, some of whom had also had phrenicectomy performed. Cough causes a change in the capacity of the thorax, which in turn causes a variation in intrapulmonary pressure, and this can be accurately measured by a manometer connected with the pleural cavity, provided that there is no fluid effusion complicating the pneumothorax and that the pleuræ are normal. There were available a few patients undergoing bilateral pneumothorax who had also had a phrenicectomy performed on one side; these gave additional valuable information. The method used was simple. Before a routine refill of the pneumothorax was given the needle in the pleural cavity was attached to a special recording manometer, in which chloroform was used as the moving fluid column. The cooperation of the patient enabled cough of varying strength and frequency to be studied, and added interest was given to the results by the study of cough in patients with various pathological conditions of the lung.

Coryllos believes that cough consists of three phases: inspiratory, compressive and expulsive. Obviously, if the diaphragm is paralysed, the thoracic capacity is lessened, and therefore less air is available for the act of coughing. Added pathological states, such as consolidation and effusion, will still further lessen the force available. Coryllos presents proof that during the second or compressive stage the diaphragm contracts, thereby checking the rise of the abdominal viscera into the chest and favouring the rising of the intrapulmonary air pressure necessary for effective cough. During the expulsive stage the diaphragm exerts a still more evident checking or restraining influence and ensures the rigidity of the floor of the thorax. The author believes that in this way the diaphragm, acting as an antagonist to the abdominal muscles, can regulate the strength and duration of cough to the particular needs of the moment. He points out in this connexion that when the intact diaphragm is watched on the fluorescent screen during successive acts of coughing, it is seen to ascend higher

[1] *The American Journal of the Medical Sciences*, ..., 1937.

with each cough, whereas the paralysed leaflet leaps up and falls back each time.

The conclusions to be drawn from this article are that there is a prevailing confusion concerning the mechanism of coughing and other similar expulsive expiratory acts; that a new concept is possible in which the diaphragm is regarded as a regulator in the strength of the expulsive force of cough needed to overcome the resistance of material lodged in the air passages, and that the diaphragm is active during the three phases of cough described above. The author has presented a coherent picture of this important physiological process, and one that is worthy of study whenever a deliberate paralysis of the diaphragm is planned. Coryllos points out that his hypothesis of diaphragmatic action indicates how both time and energy are saved during expulsive expiratory acts, and this idea is certainly in harmony with the general physiological laws which conserve the forces necessary to deal with the various episodes and emergencies arising in the animal economy.

PYREXIAL THERAPY.

A MOST extensive literature has accumulated concerning treatment by pyrexia, and many and various are the diseased conditions for which it is employed. The time is certainly fitting for our knowledge of the subject to be reviewed and systematized. E. E. Shepley makes a brief but praiseworthy effort to do so.[1] Shepley reminds us that the temperature of the human body may easily be raised above the normal in many ways. Heat may be produced externally or generated in the bodily tissues. Among the external methods may be included hot water and steam baths, electric and infra-red ray baths, and the electric blanket. What may be termed the group of internal methods includes diathermy, inductothermy, non-specific protein therapy and controlled inoculation with malaria. External heat is not suited to the production and maintenance of prolonged fever, as it is too exhausting and not without actual peril. Artificial fever is obtained by the use of penetrating heat, such as diathermy or inductothermy. In diathermy heat is produced in the tissues because of the resistance that they offer to the passage of the high frequency current as it traverses the tissues between large metal electrodes firmly applied to the skin on opposite sides of the patient's body. In inductothermy a much higher frequency is used. This current is passed through a large single coil placed close to the patient, but with no direct skin contact. As the heat production is within the body, this method more closely approximates normal. Experimental work with the inductotherm and saline solutions shows that normal saline solution (0·85%) has the same electrical conductivity as blood plasma. The conductivity of the skin, adipose tissue and muscle equals that of saline solutions of lesser concentrations. As blood plasma is more conductive than all other body tissues, it is here that the greatest heat is evoked. The reverse holds for diathermy, thus explaining the discomfort sometimes experienced from such treatment. The biochemical reactions attendant upon pyrexial therapy are of the highest practical importance. In general the effects of fever therapy resemble those of natural fever. MacCallum has observed that fever is a beneficial reaction in that the production of immune bodies proceeds best in the presence of high temperatures and that fever processes become of advantage in that they are without doubt associated with the production of substances which combat injurious agencies that have invaded the body.

Shepley discusses the various biochemical phenomena attendant upon fever therapy, and he states that when very high temperatures are produced over lengthy periods there may be seen evidence in the tissues of intense peripheral hyperæmia and sometimes focal hæmorrhages. Cloudy swelling and fatty degeneration may be observed in parenchymal cells. Depletion of glycogen may be noted and evidence of hyperplasia is not uncommon. A maintained temperature of 105° F. causes no abnormal lesions. During treatment the nail beds exhibit an enormous increase in the size and number of visible capillaries and the rate of flow is greatly increased. Such a conspicuous change in the character of the local capillary circulation must profoundly influence local metabolic processes, and degenerative tissue changes must be effectively combated. These tissue reactions are identical with those occurring in malarial treatment and in the course of the more acute infectious disorders. Shepley informs us that during a major fever treatment large quantities of sweat are lost and much sodium chloride is excreted. He administers salt to compensate for an excessive loss of sodium chloride. He admits that electropyrexia is not entirely without danger unless properly carried out, when it becomes free of all danger. This contrasts with a 5% to 10% mortality from malarial therapy. When physical resistance has been conspicuously reduced by chronic disease, care is essential with any form of fever therapy. Shepley mentions the various diseases that have been treated by fever therapy. Generally speaking, these diseases have a common factor in that they are not self-limiting and are not associated with a greatly sustained increase in temperature. Shepley informs us also that inductotherapy often gives spectacular results in both lobar pneumonia and bronchopneumonia.

To sum up, it may be concluded that pyrexial therapy by inductothermy has become almost a method of precision, compared with which malarial inoculations and non-specific protein therapy seem almost haphazard. Possibly these latter methods will soon become obsolete.

[1] *The Canadian Medical Association Journal*, October, 1937.

Abstracts from Current Medical Literature.

DERMATOLOGY.

Warts.

J. M. HUTTON (*Urologic and Cutaneous Review*, October, 1937) describes an original treatment for warts. He first reviews some facts relative to the cause, development and behaviour of warts. He enumerates under six headings the various methods at present employed for the removal of warts. The first method is removal of the wart with sufficient surrounding tissue to prevent recurrence; this is accomplished by scalpel, actual cautery or high frequency electrode. The second method is resection of the wart by strong antiseptics or caustics, such as nitric acid or formalin. Thirdly, the underlying cutaneous structures may be injured by pressure or friction sufficient to cause bleeding; the wart may then disappear. The fourth method is destruction of the blood supply of the wart by fulguration, electro-desiccation, electro-fulguration and perhaps by X rays or radium. Fifthly, a change may take place in the resistance of the host. Although the explanation of the changes which may occur in the local resistance of the skin is highly speculative, this group is included to explain the cures which sometimes follow the administration of oral, intramuscular or intravenous medications. The warts may disappear as a result of suggestion or through psychic influence, as reported by Block, Bonjour and many others. The author's treatment comes under the fourth heading, and consists in the injection of a few minims of a sclerosing agent, such as: (i) quinine and urethane solution, (ii) 50% invert sugar solution, (iii) solution of equal parts of 50% dextrose and 30% sodium chloride, (iv) 2% sodium morrhuate solution, (v) potassium oleate solution, 5% or 10%. The author prefers 50% sugar solutions. In his technique he uses a tuberculin syringe. The needle is carefully passed into the wart until the point is approximately at the junction of the base of the wart and the underlying corium. This is important, because if the solution is injected into the cutaneous structures underneath the base of the wart a sharp pain is felt, which lasts a few hours, then the sclerosing fluid is absorbed without any noticeable change in the wart; or it may remain localized and cause a slough of the wart with some of the surrounding tissue. Only a few minims of the sclerosing fluid are injected, the quantity varying with the size of the wart. The injection of the sclerosing fluid into the base of the wart is followed by immediate blanching of a small area of the surrounding skin, quite similar in appearance to the changes produced by an intracutaneous injection of a solution of local anæsthetic containing adrenaline. Within a few hours this ischæmic area becomes hæmorrhagic, with no fading of colour when pressure is applied to the area. The hæmorrhagic area subsequently undergoes the characteristic colour changes observed in any extravasation of blood into cutaneous tissues. During the following few days the wart becomes dry and hard and shows a noticeable decrease in size, with an appearance much like that following electrocoagulation. At this stage the wart may be trimmed without any bleeding being produced. Within fourteen days or longer, according to the size of the wart, it separates from the underlying structures and can be removed, a normal cutaneous surface being left. The injection treatment is described not as a cure-all, but as an additional therapeutic measure, the successful application of which depends to a considerable degree upon experience in clinical judgement and adequate skill in technical procedure. The author uses the measure extensively in subunguinal and plantar warts, and in the latter type the patient can walk about quite comfortably.

The Treatment of Pruritus Vulvæ and of Pruritus Senilis.

LEO N. ELSON (*Urologic and Cutaneous Review*, October, 1937) gives his experience of the use of ovarian extract in the treatment of *pruritus vulvæ* and *pruritus senilis*. After sixteen years' clinical experience in both these diseases he has not had one failure with ovarian extract. He states that *pruritus vulvæ* and *pruritus senilis* are degenerative neuritides. Degeneration in the nerve sheath causes disturbance in the oxidative processes of the neurone. If the process is a hyperoxæmia, it causes pain; if an anoxæmia, it causes itch. No matter what the underlying cause may be—whether infective, traumatic, climacteric, senescent or idiopathic—the pathology is the same, namely, a deficiency, a break or a degeneration in the insulation mechanism (nerve sheath), leaving the nerve axone exposed. As the ovary contains the necessary hormones for the generation of nerves it must also regenerate them, and it is on this theory that the author founded his treatment and has had success in brachial neuritis and in arthritis of the menopause. Orchitic extract is of no use in the male suffering from pruritus, but ovarian extract is equally effective in either sex. Ovarian extract is of no value in *pruritus ani*, which the author clears up by washing the part with soap and water and applying an ointment containing 30% calomel. In *pruritus vulvæ* due to *diabetes mellitus*, which is usually associated with *kraurosis vulvæ* in old women, the kraurosis disappears after treatment for diabetes, but the pruritic phase persists and has to be treated. In all cases the author administers five grains of ovarian extract three times the first day, one hour before meals, twice the second day, and once the third day. He repeats this cycle for many months until cure is effected. Local applications he has not found of much use, the best in his opinion being one containing carbolic acid, spirit of peppermint, bicarbonate of soda and distilled witch hazel.

Thymol Therapy in Actinomycosis.

SOME years ago the fungicidal properties of thymol and its liquid isomer carvacrol were shown by the fact that a one in one thousand aqueous solution killed actinomyces in forty-five seconds. This toxicity suggested a therapeutic value, and Harold B. Myers (*The Journal of the American Medical Association*, May 29, 1937) now reports the benefit of its use in six cases. Thymol was applied locally whenever possible in olive oil solution from 10% to 20% in strength. Systemic therapy is also advisable in attacking the infection and preventing its spread to other parts of the body. Thymol may be given in crystal form in capsules, one gramme a day, in order to obtain a peak load in the circulation. It should be given on an empty stomach to avoid retention and irritation of the stomach and, furthermore, to speed up absorption and obtain as high a concentration as possible in the blood. A glass of milk may be given to minimize gastric irritation. Five patients recovered; three had the infection involving the region of the jaw, one the shoulder, and one the lungs. The sixth patient was suffering from an actinomycotic lesion in the right groin, and this eventually healed with local treatment; death was due to an actinomycotic empyema and abscess of the left lung, the patient refusing to take thymol by mouth on account of gastric irritation.

UROLOGY.

Insufficiency of the Vesical Sphincter in the Female.

G. MARION (*Journal d'urologie*, March, 1937) discusses the cases in which the vesical sphincter in the female is so weak that urine trickles away when the patient is upright, though it is well retained when she is recumbent. Incontinence also appears during certain muscular efforts, also in coughing or sneezing. Such insufficiency is frequently accompanied by genital prolapse, and operations for the latter are often expected to cure the incontinence. However, it will usually be found that repair of the vesical sphincter is necessary. The technique advised by Marion for this purpose is as follows. A number 16 F. de Pezzer catheter is passed into the bladder; the expanded end, pulled down firmly against the bladder neck, serves as palpatory guide to the latter. A transverse incision is made through the mucosa of the vestibule, a little behind the external meatus. The

lower lip of this incision is dissected up, and the dissection is continued so as to separate the vaginal wall from the urethra until the end of the catheter is felt. At this point the fibro-muscular tissues on each side are brought strongly together by mattress sutures of fine linen thread, one just distal to the internal meatus and another a little more distal still. If it is possible to find the anterior borders of the *levatores ani* at each side, they may be brought together over the previous line of suture. The patient's bowels are not allowed to open for five to six days, to secure immobility of all the tissues concerned in the operation. The de Pezzer catheter is kept draining continuously. It is syringed through if it becomes blocked. Should patency of the catheter not be maintained, the catheter will have to be removed; but it should not be reinserted, an ordinary cylindrical catheter being used instead. An iodoform gauze tampon is placed in the vagina after the operation and is removed after five days. The superficial, that is, the mucosal, sutures are removed in ten days, and the catheter on the twelfth day. It may be found that the patient cannot urinate for several days, so that it may be necessary to empty the bladder with a small catheter every eight hours during this period.

Decapsulation in Urinary Stasis.

V. TRAVAGLINI (*Urologia*, June, 1937) gives an interim report on shadows made in dogs to determine the effect of decapsulation of the kidney on renal vascularization and renal efficiency in urinary stasis. One ureter was ligatured, and after a variable number of months the corresponding kidney was decapsulated. Later, the organ was removed and injected with vermilion so that the arterial and venous circulations could be separately studied by radiography of the specimen. Previously, studies of the renal function by blood chemistry, phenolsulphonephthalein secretion *et cetera*, were made on the same organ. As a control the untouched opposite kidney was simply decapsulated, there being no urinary stasis on this side. Comparisons in vascularization and functional capacity could thus be made between the two sides. Diminution and disappearance of many renal vessels on the side of the ureteric ligature were observed, as well as diminution of function. Subsequent decapsulation did not improve matters at all, and in many cases the vascular and functional state became worse after decapsulation, contrary to what appears when an unobstructed kidney is decapsulated.

Vaginal Ureterolithotomy.

C. C. HIGGINS (*Urologic and Cutaneous Review*, September, 1937) remarks that vaginal ureterolithotomy has never been favoured greatly by surgeons. He considers that the indications are as follows. A calculus in the ureter, palpable *per vaginam*, may be removed by the vaginal route, especially in obese parous women, in whom extraperitoneal abdominal operation is very difficult. In nonparous women "in good physical condition" the abdominal route is preferable but not essential. Occasionally when the stone is not palpable it may be removed satisfactorily by the vaginal route. Vaginal ureterolithotomy is particularly useful in patients who are dangerously ill. Two operative techniques are described; both have been successfully employed. Complications are rare, and are avoided by accurate anatomical knowledge. Uretero-vaginal fistula did not occur in the author's series of eleven cases. There was no mortality, and the duration of the patients' stay in hospital was considerably shortened.

Post-Operative Management in Tuberculosis of the Kidney and Bladder.

J. A. LAZARUS (*Urologic and Cutaneous Review*, August, 1937) draws attention to the statistics of the results of treatment in urinary tuberculosis. In unilateral renal tuberculosis with nephrectomy the immediate mortality is 4% to 7%. Half of the patients are permanently cured, 15% show progressive symptoms, while 30% are dead within five years. Of patients with bilateral disease, 84% died. The author is particularly concerned with the number of persistent fistulæ after operation. Several suggested causes have been disproved. The ureteral stump has little or no influence on the production of post-operative sinuses, nor does the presence of perirenal fat influence their development. It appears more probable that chronicity favours primary healing, whereas an acute process in the kidney is more likely to lead to sinus formation. Prophylactically the author uses: (i) hygienic and constitutional measures similar to those used in pulmonary tuberculosis; (ii) ultra-violet light therapy; (iii) deep Röntgen therapy; (iv) surgical technique which incurs the minimal amount of damage to the tissues. Dakin's solution is applied to the wound if any unusual discharge is present. In forty-seven cases he has had only three fistulæ. These cases were healed by the above methods, but the author states that "this routine of treatment has not been found to possess any particular advantage over the methods employed by others". For vesical pain following nephrectomy deep Röntgen therapy has been found to be most efficacious. Both ultra-violet and Röntgen irradiation should be commenced soon after operation, as their virtue lies in preventing rather than curing sinuses.

The So-Called Pyelo-Renal Reflux.

A. JASIENSKI (*Journal d'urologie*, February, 1937) considers that the terms pyelovenous, pyelotubular and pyelolymphatic reflux, referred to a renal phenomenon in conditions of raised intrapelvic pressure, do not correspond to reality. He thinks that in all such cases of raised pressure the fluid percolates into the connective tissue of the renal parenchyma, and in severe cases finds its way to the loose space under the capsule, where it awaits reabsorption.

Gynæcological Correlations in Urology.

A. PATANIA (*Urologie*, March, 1937), in discussing gynæcological conditions and urology, first of all considers pyelitis of pregnancy. In these cases three groups can roughly be distinguished: (i) cases with mild development and absence of fever in which cure can be effected by simple treatment; (ii) cases of moderate gravity, with elevations of temperature, in which the retained ureteric catheter, properly applied at the right time, leads to cure; and (iii) severe cases, too far advanced to be favourably affected by the retained catheter, in which the clinical picture is that of suppurative pyelonephritis, and in which renal decapsulation is the method of choice. The author considers that the fact that interruption of pregnancy was obligatory in only 9% of 157 cases is a testimony to the value of the above set of indications. The course of most preexisting urological lesions is aggravated by pregnancy; treatment in such cases should be just what it would be if pregnancy did not exist. When a pyosalpinx perforates into the bladder, spontaneous cure follows in the majority of cases, so that operative intervention is not called for, except in those cases which resist conservative treatment for six to eight weeks, and in which, from the beginning, a tuberculous lesion is suspected. Cystoscopy is considered obligatory before certain important gynæcological operations, especially operations for malignant tumours of the uterus, when bulbous œdema indicates invasion of the vesical wall. Ureteric catheterization is necessary from the prophylactic point of view before such difficult operations as panhysterectomy or the extirpation of an intraligamentary ovarian cyst.

The Effect of Surgical Drainage on "Functionless" Kidneys.

M. G. SCHULOF (*Surgery, Gynecology and Obstetrics*, August, 1937) has investigated the effect of surgical drainage on kidneys which have been functionless as a result of tests of renal function. He refers to the contention of Hinman that rehabilitation of such kidneys does not take place. He has made an intensive study of ten among forty cases in which surgical drainage was established in apparently functionless kidneys. In each instance renal function was promoted. In four instances the drained kidney functioned equally as well as the opposite kidney; in five instances function returned to approximately 50% of that of the other side; in one instance function returned to the extent that "good visualization was delayed to the sixty-minute intravenous urogram".

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on September 23, 1937, in the Robert H. Todd Assembly Hall, British Medical Association House, 135, Macquarie Street, Sydney, DR. L. A. DEY, the President, in the chair.

The Use and Abuse of Vaccine Therapy.

PROFESSOR H. K. WARD, in opening a discussion on the use and abuse of vaccines, briefly traced the history of vaccines. He said that the vaccinia of Edward Jenner was an empirical though very valuable discovery, and the principle underlying it was not really understood until Pasteur demonstrated that chickens could be protected against chicken cholera by injecting them with an attenuated living culture of the chicken cholera organism. Pasteur exploited this method of immunization with living attenuated cultures in anthrax and rabies, and it is the dominant motif in French bacteriology. It was seen in Calmette and Guérin's work on immunization against tuberculosis with the attenuated strain "B.C.G." of the tubercle bacillus. It was seen in Levaditi's attempts to attenuate the *Treponema pallidum*, so far unsuccessful. This method had proved so fruitful that other workers in other countries followed on in the "Pasteurian tradition", as the French writers referred to it, and recent attempts to control yellow fever and plague in this manner had given promising results. Now that Burnet and other workers had shown that it was possible to attenuate the influenza virus, there was reason to hope that prophylactic immunization might prove to be a practical measure in the case of influenza also. At the beginning of this century Almroth Wright had shown that the injection of dead typhoid bacilli was an efficient prophylactic measure against typhoid fever, and his technique of injecting killed organisms, which of course carried no risk, had been used in attempts to prevent a number of infectious diseases—not with a great measure of success.

Wright subsequently turned his attention to the therapeutic use of vaccines, and largely by his work this method of treating infectious disease had come into favour. In the first few years an attempt had been made to control the effect of these specific therapeutic vaccines by an estimation of what Wright called the opsonic index. The errors inherent in the technique of this test were at least as great as the differences that were being measured, and the estimation of the opsonic index had been abandoned. However, therapeutic vaccines remained, although not unchallenged. Indeed, it might be said that their advocates were definitely on the defensive.

Professor Ward said that he did not believe that vaccines had any specific therapeutic value, and pointed out that quite apart from the fact that it was illogical to inject more organisms into a patient already infected, it was curious that the value of therapeutic vaccines was not more firmly established after thirty years' experience, and it was still more curious that there was no definite evidence in animal experiments in favour of their use. In contrast to this lack of evidence in the case of therapeutic vaccines in controlled animal experiments, there was ample evidence in favour of the therapeutic use of "Prontosil" in animals infected with certain organisms, and that evidence had been obtained in the space of a few months.

Professor Ward, after reviewing the evidence concerning the use of vaccines in the treatment of staphylococcal infections, whooping cough, rheumatoid arthritis *et cetera*, said that the advocates of these vaccines were often enthusiastic, but he would like to see more controlled evidence and less enthusiasm. There was another vaccine that was widely used and had no valid evidence behind it, and that was the common cold vaccine. At least two well-controlled experiments had been carried out on an adequate number of volunteers, and there was not the least indication that the injection of the vaccine prevented the common cold. There was also no evidence that the organisms in the vaccine had any etiological relationship to the common cold

Professor Ward also made reference to the claims of certain proprietary preparations, not necessarily vaccines, in the treatment of infectious diseases. The proprietors of these preparations made extravagant claims of their value and deluged the profession with propaganda. He urged the New South Wales Branch to make representations to the Parent Body concerning the desirability of setting up an authoritative committee whose function it would be to investigate the claims of proprietary preparations, and after such investigation to report the result in full in *The British Medical Journal*. Such reports would be a boon to the practitioner who had neither the time nor the training nor the equipment to carry out such investigations himself. It might be said that this would be too formidable a task for the Association to undertake. To that it could be answered that if the American Medical Association could carry it out, surely it was not beyond the powers of the British Medical Association.

DR. A. H. TEBBUTT said that from his point of view the subject was a difficult and perhaps unfortunate one, and he did not quite know how to discuss Professor Ward's remarks. He did, however, wish to thank him for his fine but hardly unprejudiced address, with no soft words. He agreed with a lot that had been said, and disagreed with some. In practice, vaccines were of two kinds: specific vaccines and non-specific vaccines. Specific vaccines were those used when a patient received the antigen of the organisms with which he was infected; non-specific vaccines were those used when the antigen used was not the antigen of the organism causing the infection. Professor Ward had referred to Pasteur and Wright, but with a marked contrast. Wright's pioneer work with typhoid vaccine, however, was outstanding work, and showed that inoculation of dead organisms produced results comparable with Pasteur's inoculation of attenuated organisms. Vaccines had been used in both acute, chronic and recurrent infections. Perhaps much could not be expected from the use of vaccines in acute conditions; but favourable reports had appeared on acute diseases (typhoid fever, pneumonia *et cetera*) in which vaccines had been used. Typhoid fever had been so treated in Australia, but the work had apparently been discontinued. In chronic or recurrent infections, Dr. Tebbutt said, the use of vaccines was rather a different matter. It was not a pathologist's job to treat patients, and so he only knew of results from the clinician, but it should be possible to increase the immune state, for example against the staphylococci, in some people, if not in all, and he believed that some clinicians found that this was so. Referring to vaccination against colds, Dr. Tebbutt said that good results had been obtained by this procedure, patients in some instances having been free for some two or three years afterwards. Upper respiratory tract infections were not all due to viruses. Thomson, of London, held that bacteria, pneumococci, influenza bacilli *et cetera* were often responsible, and from his own experience he would agree. Combinations of common cold virus and respiratory tract bacteria probably occurred.

Speaking of non-specific vaccine therapy, Dr. Tebbutt said that in nearly all diseases of joints, ligaments *et cetera*, and in the rheumatic diseases, vaccine treatment was non-specific. Whether these non-specific vaccines did good or not was for the clinician to determine. The only effect could be some sort of non-specific effect. Dr. Tebbutt agreed with Professor Ward that it was a "shot in the dark". It was the clinician's responsibility to discover what did good to his patient. In conclusion, Dr. Tebbutt once more said that he had enjoyed the humour of Professor Ward's iconoclastic address.

DR. HAROLD RITCHIE said that he felt that someone else should have spoken before him, because he gave very few vaccines. He wished to compliment Professor Ward on his address, and also to make a few criticisms. He said that he believed vaccines of certain organisms to be of value in certain chronic diseases, such as colon pyelitis. He did not believe that B.C.C. vaccine cured the pyelitis, but by

the judicious use of vaccine immunity might be raised to such a point that exacerbations were not severe enough to cause any noticeable general reaction. Vaccines *plus* general treatment for the improvement of the patient's health, such as the administration of drugs by mouth, *et cetera*, might terminate the illness. With regard to furunculosis, Dr. Ritchie said that he had no faith whatever in the use of vaccine therapy; in diseases with many remedies there was no cure. The patient's immunity was gradually rising, or the local conditions causing the furunculosis were disappearing, and the last treatment to be used was given the credit for the cure. Dr. Ritchie felt that Professor Ward had been a little unkind to the bacteriologist when he slid over the value of prophylactic vaccine therapy. Some vaccines had a great value, as had been proved by the results of their use on active service. With regard to rheumatoid disease, he felt impelled to agree with Dr. Tebbutt; no specific organism was proved to be responsible, but some form of "shock" therapy was sometimes of great value. He had seen many examples of a great deal of good being done. He concluded by saying that he would leave the cudgels to someone who gave vaccines more often and more hopefully than himself.

DR. C. H. SHEARMAN also expressed his thanks to Professor Ward for his address, and said that he wished to speak generally rather than specifically. He thought that Professor Ward had been a little hard. It was known that immunity could be conferred by prophylactic vaccines, and therefore it could reasonably be supposed that immunity could also be raised by therapeutic vaccines. It might be argued that there was no need to give the antigen, because the patient was already infected in acute infections; but perhaps a metaplasia of the tissues occurred which might prevent the absorption of antigen, and the addition of a vaccine might speed up the production of antibodies. It was necessary to provide a specific antigen, and in those patients who responded to vaccine therapy the specific antigen had probably been provided; in those who did not it might not have been provided. A judgement based on figures would be fallacious, because figures could prove anything. Clinicians had not provided enough experimental evidence to enable the scientific value of vaccines in therapy to be judged. In conclusion, Dr. Shearman made a plea for more knowledge of the antigenic value of vaccines and more evidence from clinicians of their value in treatment. Therapeutic vaccines had stood the test of time, he pointed out, and consequently one would expect them to have some clinical value.

DR. F. S. HANSMAN said that he wished to challenge Professor Ward's logic, believing him to be assailable. No one knew everything about immunology. Had the true value of whooping cough vaccine really been discovered? In the first year of its use the vaccine had been considered to have done good; in the next year the results had not been considered good; for the last two or three years good results were obtained. Either the virulence of the organism varied or the vaccine did good; he wondered which was the explanation. He was very surprised that vaccine therapy had been dropped in America, as he had learned from *The Journal of the American Medical Association*. The journal, however, was not always infallible; it had condemned the oral use of pituitary extract, and this had been proved to do good. No one, prior to the Bundaberg catastrophe, would have believed that all was not known about the staphylococcus; the catastrophe proved that the staphylococcus produced toxins. Speaking of colds, Dr. Hansman said that they seemed to be partly due to organisms, and it was possible that, even if antibodies could not be demonstrated in the blood, all the immunological processes of the body were not known. The substances involved might not be those of which medical practitioners were already aware. In conclusion, Dr. Hansman said that he considered that nothing should be condemned before it was proved wrong or right, and that data should be carefully collected.

DR. B. W. STEVENSON said that he had hoped that Professor Ward would refer to diphtheria immunization. Professor Ward had mentioned whooping cough vaccine as being of no use; he himself had found that it had no noticeably beneficial effect, and he did not consider it of any real use therapeutically. Dr. Hansman's remarks had partly altered his opinion. If what Professor Ward said was true, medical practitioners were unwittingly humbugging the public by using the vaccine. Dr. Stevenson wondered whether a resolution should be made by those present to refrain from using whooping cough vaccine.

DR. F. S. STUCKEY said that he wished to speak for the body of general practitioners, who had little opportunity for experimenting with controls. There was one suggestion that he would like to make. Was it not possible, in the use of vaccines in cases of acute sickness, that injections of endotoxins might augment or accelerate the activity of the defensive mechanisms of the body and the production of antibodies, although organisms might be present in the body already? The use of vaccines might be quite justifiable even in acute infections. Dr. Stuckey said that he would appeal to his own experience for examples. At the time of the pandemic of pneumonic influenza he was at Inverell. The great majority of people there had protective vaccination with the vaccine issued at that time. Some of the outlying centres could not follow this example to the same extent as Inverell did. The outcome was that when the pandemic reached the district a greater number of deaths and a greater number of cases occurred in the unprotected areas than in Inverell itself, which had a much larger population. Dr. Stuckey said that this experience had confirmed the belief that he already held in the value of vaccine. When whooping cough vaccine was first issued, he had used it with some diffidence. He felt satisfied that it justified its use by determining the lesser frequency of the paroxysms, until he found a child to whom it seemed to be of no value at all. However, the mother was sure that the vaccine had been of considerable benefit to that child, compared with her experience with her other children, who had no vaccine treatment. Dr. Stuckey said that he had continued to use vaccine.

DR. JOHN HALLIDAY thanked Professor Ward for his address, and said that he felt that part of the present-day situation with regard to the clinician had arisen because some of Professor Ward's predecessors had not read Francis Bacon. The clinician was overwhelmed by a mass of vaccines, attenuated cultures, and so on, and tended to over-estimate their usefulness. However, he felt that they had been brought into practice on the authority of the scientific branch of the profession, and that naturally they died rather hard. Few clinicians really had much faith in vaccine therapy as a specific form of treatment; most used it for want of better. If clinicians felt that their patients, particularly of the rheumatoid group, improved after this type of treatment, they were at the present time not justified in withholding it.

DR. LORIMER DODS said that he was glad that Professor Ward had denied the value of therapeutic vaccine in the treatment of whooping cough. He asked Professor Ward's opinion on the prophylactic use of smooth strain pertussis vaccine, and he wondered whether such a vaccine would be provided in the near future by the Commonwealth Serum Laboratories.

DR. COTTER HARVEY referred to "shock" therapy, mentioned by Dr. Ritchie. Dr. Harvey thought that there might be some use in giving by injection substances to arouse the patient's resistance. One question was: could vaccine raise the patient's resistance in acute infections? Some forms of "shock" therapy had the weight of clinical evidence behind them, but in the laboratory it might not be considered correct.

DR. NEVILLE DAVIS thought that therapeutic vaccines had been to a very large extent disappointing. That vaccines were of help in the treatment of acute diseases was a statement put forward by many people. The immunological defences of the body were commonly spoken of; Dr. Davis wished to know by what yardstick they were measured. Few yardsticks appeared to measure thirty-six inches to the yard. It was difficult to assess the value of any particular form of treatment; the pathologist differed from the bacteriologist. The bacteriologist gave what help he could, an opinion, which might prove to be

valueless, even though given with the best intentions in the world. The pathologist dealt with tissue removed from the body frequently when the patient was dead; his opinion was more definite. It was for the bacteriologist to justify his existence.

DR. P. FIASCHI said he had had some experience of vaccines in Neisserian urethral infections in males. He considered the gonorrhœal vaccines of little or no value, and had used them in conjunction with local treatment without any improvement in the end results. He had seen many patients treated by other practitioners with vaccines and liberally punctured without any benefit. Many of the gonococcal vaccines were quite painful, and clients refused to have them. Vaccines, in his opinion, did not compare with the use of "606" derivatives, as advocated by Levy-Bing, of Paris, a number of years earlier in the treatment of complications of gonorrhœa.

Professor Ward, in reply, said that the subject was controversial; there were many opinions, but very few facts. Dr. Tebbutt had referred to the good results of vaccine treatment; Professor Ward wondered whether anyone present had used it in bacterial endocarditis, a disease with a heavy mortality, and one in which there was ample scope for vaccines to prove their usefulness. He pointed out that successes were spoken of and failures forgotten. The difficulty, however, was that he had no definite negative evidence, any more than others had any definite positive evidence.

In reply to Dr. Ritchie, Professor Ward said that the use of "Prontosil" in colon pyelitis had recently been reported on favourably. He would be the last to deny the value of prophylactic vaccines, but he understood he had been asked to discuss only therapeutic vaccines. With regard to the use of non-specific vaccine in rheumatoid arthritis, Professor Ward said that there was some response to injections of foreign substances, but there were a very large number of remedies for rheumatoid arthritis, most of which, according to reports, had about 75% success. It was necessary to be careful about ascribing any improvement to non-specific therapy, for other measures employed might be bringing about the improvement.

In reply to Dr. Shearman, who had inferred that if vaccines were valuable prophylactically they must be useful therapeutically, Professor Ward said that if a rabbit was given a pneumococcal vaccine and then an injection of living organisms four days later, it would show no sign of infection; if it was given the vaccine after an injection of living organisms, it would become infected and would almost certainly die. This showed the difference between prophylactic and therapeutic vaccine. Therapeutic vaccine had to be used after infection had taken place. There were really three categories of therapeutic agents. With the first kind, such as insulin and "Salvarsan", the results could be predicted. With the second kind of therapeutic agent, used in diseases like pneumonia, in which the patient lived or died, there was some chance of assessing the results of treatment. With the third kind of agent used in such conditions as rheumatoid arthritis, it was very difficult to assess clinically whether the patient was better or not; the correct way was to get someone who did not know what had been done to the patient to assess the state of the patient's health. That was the only way to assess scientifically the value of treatment.

In reply to Dr. Hansman, who had spoken about whooping cough vaccine, Professor Ward said that the Commonwealth Serum Laboratories were about to produce a "smooth" Phase I vaccine. Opinion in America was generally against the use of vaccine in the treatment of whooping cough, but he did not mean to imply that the Americans were infallible, merely that American opinion differed from Australian opinion in this matter. Scepticism as to the value of toxoid therapy in staphylococcal infections had been expressed in the previous week's issue of *The British Medical Journal*.

In reply to Dr. Stevenson, Professor Ward said that it was really not his province to speak about diphtheria immunization, but that he would be glad to do so. Everyone would like to immunize children with one "shot" instead of three "shots", which were a great nuisance. The known facts about the "one-shot" method suggested that it was fairly good, but there was considerable doubt about the duration of the immunity thus produced. Recent reports on a "two-shot" method, in which precipitated toxoid was used, had been very favourable, a high percentage of the children showing a "negative" Schick reaction eighteen months after immunization. The difficulty, however, was that Dr. Morris was unwilling to risk any possible danger of inflamed arms, and precipitated toxoid was still a little risky in this respect. Professor Ward thought that the "two-shot" method with precipitated toxoid would probably come into wide use. Occasionally "Schick-negative" children did contract diphtheria, but the case mortality was very low.

In reply to Dr. Stuckey, Professor Ward agreed that in general practice it was most difficult to work with controls, but said that a lot of such work had been done in America by Sauer in testing the value of prophylactic vaccination against whooping cough. Naturally his efforts had to be restricted within a narrow field. With regard to the influenza vaccine used some years earlier, as it was now known that the ætiological agent was a virus, he could not explain the facts reported by Dr. Stuckey.

In reply to Dr. Dods, Professor Ward said that with prophylactic vaccination against whooping cough, the duration of immunity was dubious, as there was conflicting evidence. Sauer reported that results were good, and his evidence showed that protection lasted some years. His work had been repeated by another group of bacteriologists, and they were unable to confirm Sauer's claims. Further work was evidently necessary, and Professor Ward hoped that it might be carried out in Australia by general practitioners. It would be necessary to use a suitable vaccine and to keep careful records.

In reply to Dr. Davis, Professor Ward said that if he (Dr. Davis) challenged the justification of bacteriologists to existence, he should read "The Autobiography of Benvenuto Cellini" and see how people fared in those days. What the bacteriologists had done was to eliminate a lot of noisome diseases, but preventive measures were carried out very quietly. The trouble lay in Dr. Davis expecting bacteriologists to cure diseases once contracted, which was a much more difficult matter.

A MEETING of the Victorian Branch of the British Medical Association was held at the Medical Society Hall, East Melbourne, on November 10, 1937, PROFESSOR R. MARSHALL ALLAN, the President, in the chair.

Resuscitation of the Apparently Drowned.

The meeting took the form of a discussion on the subject of resuscitation of the apparently drowned. Mr. E. A. Pleydell, the Secretary of the Victorian Branch of the Royal Life Saving Society, was present and addressed the meeting. A party of life-savers gave a demonstration of life-saving drill and of methods of release and resuscitation.

DR. THOMAS KING, the Honorary Medical Officer of the Victorian Branch of the Royal Life Saving Society, opened the discussion. He said that the first recorded cases of resuscitation indicated that it had occurred in Oxford as far back as 1650. In 1767 Réaumur effected the recovery from drowning of several people in Switzerland. Shortly afterwards a society was formed in Amsterdam to investigate the subject of recovery, to instruct people in the best methods and to reward them for their services on behalf of the apparently drowned. In 1774 Mr. William Tossack, a surgeon, reported the recovery of a man dead in appearance; the surgeon opened the man's mouth, covered it with a linen handkerchief, and blew with great force down the throat, distending the lungs and bringing about restoration of respiration. In 1773 Dr. A. Johnson had suggested the formation in England of a society similar to that in Amsterdam, and Dr. Hawes had advertised that he would reward persons who rescued drowning people between Westminster Bridge and London Bridge and brought them to certain stations on the river bank appointed for resuscitation. There was strong feeling

against this procedure, as it savoured of human presumption in bringing the dead to life. However, the Royal Humane Society was founded as the outcome of these efforts, and the patronage of Royalty soon overcame the scruples of the people and led to the patronage of many prominent persons. The system of inducing artificial respiration then in vogue was to force air into the lungs by means of a pair of bellows, the pipe of which was inserted into one nostril while the other nostril was held closed. By pressure on the chest air was expelled and respiration was thus imitated by alternating the intake and output of air. Dr. King stated that two outfits for the purpose, dating back to 1782, were at present in the museum of the Royal College of Surgeons of England. Dr. Hawes had the individual supported on a cradle and hoisted over a furnace as a powerful stimulant to restore animation. Other aids to recovery were holding up by the heels, rolling on large wine casks, and bleeding. In 1856 Dr. Marshall-Hall introduced the method known by his name, which consisted of applying pressure between the shoulder blades and rolling the patient from side to side at the rate of fifteen times a minute.

In 1869 Dr. Howard propounded another method, in which pressure was applied by the hands of the operator to the lower ribs with the patient lying on the back, this resembling in many ways the method still used for attempted restoration of breathing on the operating table.

In 1857 Dr. Silvester introduced the method known by his name. With the patient on the back, his arms were pulled up above the head, the chest being thereby inflated; they were then pulled down, folded and pressed against the sides of the chest, deflating it. Prolonged repetition of these movements was very tiring for the operator.

In 1903, after physiological experimentation, Professor Schäfer described a new method. It differed from the others in that the patient lay on the face, thereby avoiding the necessity of having the tongue attended to and ensuring the escape of mucus and fluid from the chest through the mouth. In addition, artificial respiration could be commenced without delay. The pressure of the abdominal organs against the diaphragm during the pressure on the chest drove air out of the lungs. Dr. King emphasized the point that the Schäfer method was the only one which was advocated at the present day by the Royal Life Saving Society. He also referred to the new method, the Höljer-Neilson, which resembled the Silvester method, with the exception that the patient's face was downwards to the ground. This method allowed of the simultaneous application of the Schäfer method by another operator. It was at present being investigated by the authorities and taught to the life-savers, but had not yet received official endorsement. Dr. King also made it plain that, when presented with a case of drowning, the life-savers were instructed to commence artificial respiration as soon as the victim was brought on shore, and to send for a doctor without delay. On arrival, the doctor was expected to take charge of the patient and to inject adrenaline or strychnine at his discretion; but the life-savers considered that it was not right for the doctor to stop them from continuing artificial respiration until all present were satisfied that life was extinct.

Dr. King said that the Royal Life Saving Society had complained through their secretary that some of the doctors they had met on the beaches during rescuing or resuscitating incidents had misunderstood the life-savers in certain respects. Some of the doctors had merely an antiquated knowledge of the methods of resuscitation, and others had not seemed to have any knowledge of the subject and had even taken steps to prevent the use of proper methods or resented that a lay person should offer an expression of opinion. Another complaint was that some doctors thought that resuscitation efforts were useless if the drowned person had been submerged for five minutes or longer.

In 1912 the underwater swimming record time had been established at Paris; the time was six minutes twenty-nine and four-fifths seconds. At other times the doctors had, in the opinions of the life-savers pronounced life extinct far too early. Dr. King at this stage read a number of letters which established evidence and examples of each of these complaints, and said that the main object of that evening's demonstration and discussion was to bring about the closest cooperation between life-savers and doctors.

Dr. King pointed out that there was always a possibility that questions of the time of submersion were inaccurately decided in the state of excitement which always existed, and the element of doubt was complicated by uncertain evidence as to the period of time of total submersion, which might be intermittent. He had not been able to satisfy himself that a recovery had ever taken place after undoubted total submersion for as long as five minutes. On the other hand, there were numerous instances on record in which life-savers had been successful in restoring animation after working for longer than one hour. He expressed the hope that the discussion would be helpful both to the Royal Life Saving Society and to the British Medical Association in clearing up misunderstandings and leading to better cooperation.

DR. IVAN MAXWELL spoke on the biochemical and physiological changes that occur during the process of drowning. He emphasized the importance of asphyxia (anoxia) as the real cause of death in this condition. He said that in treating the apparently drowned the problem was to supply oxygen to the respiratory centre, which had ceased to function. The first essential in accomplishing this was that the circulation of blood should be maintained, for if the heart had ceased to beat, and hence there was no circulation of blood to convey oxygen to the respiratory centre, then artificial respiration was invariably futile.

The respiratory centre was now regarded by physiologists as consisting of three parts: (*a*) the gasping centre, (*b*) the apneustic centre, (*c*) the pneumotaxic centre. These were coordinated in their activity by intimate neuronic connexions. In ordinary breathing the gasping centre was not used. The apneustic centre initiated inspiration, and this was terminated by the action of the pneumotaxic centre.

In drowning the pneumotaxic centre failed first, then the apneustic centre, and finally the most primitive centre—the gasping centre—ceased to function.

Restoration of respiration could rarely be induced in a person who had been completely submerged for five minutes or more.

Pearl divers could seldom remain under water for more than two minutes, and the divers of the Red Sea were usually forced to come to the surface to breathe within ninety seconds of submersion.

Dr. Maxwell said that though it had been taught in the past that anoxia (lack of oxygen) stimulated the respiratory centre directly, the experimental evidence in recent years had indicated that oxygen lack *per se* actually depressed the respiratory centre by its direct action, but it might stimulate it indirectly by its effect on the sino-aortic nerves. From the aortic arch and from the carotid sinus, impulses—generated by lack of oxygen in the blood—passed to the respiratory centre and stimulated it to activity. Excess of carbon dioxide stimulated the respiratory centre directly and also indirectly through the sino-aortic nerves.

Experiments on dogs had shown that entrance of water into the lungs played a very prominent part in causing death by drowning. Water did not penetrate to the alveoli, but became mixed with air in the bronchioles, and frothing occurred, which impeded the entrance of air during the process of artificial respiration. Furthermore, the asphyxial state induced the formation of mucus in the finer respiratory tubes, and this, mixed with air, formed an emulsion which also added to the difficulty of air entering the alveoli.

Dogs completely submerged in water for four minutes invariably died from drowning, whilst if a plug of gauze was inserted into the trachea before the dogs were submerged for four minutes, the animals lived after being removed from the water.

In conclusion, Dr. Maxwell stressed the importance of inverting the patient and making every effort to remove water from the respiratory tract before artificial respiration was commenced.

DR. C. H. MOLLISON discussed the pathological aspects of drowning. He said that the pathological appearances

varied in different cases, according to the mode of death and the length of time that had elapsed since death took place. In typical cases of drowning the mode of death was asphyxial from the inhalation of water, which was churned up with the mucus of the air passages into a fine white froth, which effectively prevented oxygenation of the blood. In those cases the heart struggled on for a varying period of time, during which efforts at resuscitation might be successful. The condition of apparent death might last for a long period, and efforts to restore animation should be continued until some indubitable sign of death was found. He thought that the earliest indubitable sign of death was the occurrence of *post mortem* staining or hypostasis, which indicated positively failure of the circulation. Dr. Mollison said that another mode of death was termed asphyxial syncope. In these cases the heart failed rapidly after a slight degree of asphyxia had been induced by entrance of some water into the upper air passages; it was necessary to postulate preexisting disease to account for the sudden heart failure. The other mode of death to be considered, Dr. Mollison termed the purely syncopal mode, where a sudden stoppage of the heart occurred from inhibition or shock. He stated that in submersion this was associated with a stimulation of the nasal mucous membrane by the entrance of water. It explained those rather puzzling cases of death in shallow water, of which he had seen several, and enumerated instances.

Dr. Mollison drew attention to the interesting remarks of Sir Bernard Spilsbury in a presidential address to the Medico-Legal Society of England in 1933, on some medico-legal aspects of shock. Sir Bernard Spilsbury had said that it was well known that bodies removed from the water not infrequently showed no signs of death from drowning and no other conditions which would account for death. In some cases of death from shock after immersion in water suicide could not be excluded. Sir Bernard Spilsbury had abandoned the view that the shock was due to the stimulus of the cold water acting on the skin in favour of the one that death was due to the shock of the sudden passage of water up the nose when persons entered the water feet first. Sir Bernard Spilsbury had referred to the fact that the pearl divers of the Persian Gulf wore no diving dress, but took the precaution of placing a clip on the nostrils before they were lowered into the sea.

Dr. Mollison quoted the opinion of the late Dr. Neild that the sudden shock or inhibition causing death must be ascribed to some perversion of the normal nervous mechanism, which might act at one time and not at another.

After stating that the asphyxial mode of death could be the only one in which efforts at resuscitation would not be futile, Dr. Mollison described the *post mortem* appearances in recent cases of drowning before any decomposition changes had occurred and when the mode of death was asphyxial. Externally there would be considerable lividity, which tended to subside to the dependent parts after the body had been lying on the back for some time. In these conditions the face, after being livid, became pale, white froth was often seen at the nostrils or could be produced there by pressure on the chest. Goose-flesh (*cutis anserina*) might be found on the skin, especially on the front of the thighs; various aquatic substances, such as weeds or sticks, might be found in the hands, and *rigor mortis* was usually more pronounced if there had been much struggling in the water. With reference to the internal *post mortem* appearances he mentioned characteristic appearances in the air passages and the lungs. The air passages would be filled with fine bubbles of white mucous froth, and the lungs would be distended and might bulge out of the chest when the breast bone was removed; the right side of the heart and the large veins would be overloaded with dark fluid blood, and the organs generally would be much congested; the stomach commonly contained water, some of which might have passed into the duodenum or jejunum. Dr. Mollison mentioned an observation of interest that had been made by Professor Gettler and was recorded in *The Journal of the American Medical Association* in 1921; he had stated that in cases of ordinary drowning there was a difference in the chloride content of the blood in the two sides of the heart. In drowning in fresh water the chloride content would be lower in the blood from the left side than in that from the right side, but in drowning in salt water the reverse would be the case. The degree of difference would depend on the length of time that had elapsed between the entrance of water into the lung and the stoppage of the circulation. Dr. Mollison commented that Yamakami, a Japanese worker, had confirmed Gettler's observation, but that the test could be used only in cases of recent drowning when other appearances would be conclusive. After a body had been in the water a few days the typical signs of drowning would have been destroyed by putrefactive changes. The water would have passed out of the lungs into the pleural cavities; the mucous froth would be replaced by coarse bubbles of putrefactive gases; the heart would be empty, and the only indication of its originally congested state would be the deep reddish-black staining of the endocardium, especially on the right side.

In conclusion, Dr. Mollison stated that in syncopal cases there were practically no signs of drowning, and in asphyxial syncope the signs would be very slight; no characteristic froth and no water would be found in the lungs.

MR. E. A. PLEYDELL, Honorary Secretary of the Royal Life Saving Society of Victoria, said that as a result of many drowning accidents in England the society was first founded in 1891 and was known as the "Swimmers Life Saving Society". Mr. W. Henry was appointed first secretary, and held the position until his death thirty-seven years later. At first the members had great difficulty in furthering the aims and objects of the society, and often were held up to ridicule by members of swimming clubs.

In 1893 His Royal Highness the Duke of York became president, and in 1894 the first branches at Manchester and Sydney were formed. His Royal Highness the Duke of York retained the position of president until he became King George V in 1910. On being called to the throne he elected Lord Desborough as permanent president.

From 1899 to 1904 quite a number of teams toured Italy, Germany and other foreign countries on the Continent, with the result that life-saving was taken up by these countries, and at the present moment forty-three foreign countries had received permission to translate the Royal Life Saving Society Handbook into their own language and were teaching the society's methods of rescue, release and resuscitation. In 1904 the society was granted permission to use the title "Royal", and in 1924 the Royal Charter of Incorporation was granted by His Majesty King George V. For the first five years of the society's existence very few awards were issued, but the movement had grown so rapidly that in the British Empire in the previous year over 100,000 awards were issued.

In Australia there was a branch of the society in each State, and as a result of a conference held in Melbourne in 1934, at which Mr. H. H. Lock, Chairman of the Central Executive, London, was present, the Australian Federal Council was formed, and this body now controlled all Royal Life Saving Society activities in Australia. All badges, certificates and medallions, previously imported from England, were thereafter manufactured in Australia.

The Victorian branch was founded in 1904, and the pioneers experienced very similar conditions to those experienced by the founders of the society in England; from 1904 to 1910 only 119 awards were gained. Since then the Victorian branch had made rapid progress, and to date 35,620 people had been taught the society's various methods of rescue, release and resuscitation, and had held its various awards.

The members of the surf clubs on the foreshore were all amateurs, and all the club-houses on the different beaches, with the exception of Williamstown and St. Kilda, had been erected by the members themselves, not one penny being made available by the Government or Council, and the position was that the Government and/or Council might terminate the occupancy of any particular club and take over the buildings by giving three months' notice. When it was realized that club-houses like Elwood, North

Road, Brighton *et cetera* were valued at over £1,200 each, those present would agree that the work of volunteers was worthy of commendation. Each club was expected to patrol that portion of the beach allotted to it, and Mr. Pleydell was pleased to say that prior to the unfortunate drowning accident at Elwood two years earlier, not one life had been lost on any patrolled beach. To give some idea of the work these patrols were doing, he said that for the previous three years 284 rescues had been effected.

With reference to the members of the clubs themselves, on joining the club a member had to pay his affiliation fee, buy his own uniform, pay for his own awards and pay his own expenses when his team visited other clubs to participate in carnivals, and of course he had to make himself available for patrol work. Each club had also to keep an up-to-date first aid chest fully equipped, and during the season many thousands of people were treated for cut feet, sunburn or any other injury they had unfortunately received no Government assistance. In 1936 the Government *gratis*. The municipalities did not as a rule assist the clubs financially, but in some cases the councils donated the sum of £5 towards the upkeep of the first aid equipment, and when it was pointed out that in some clubs this equipment cost up to £20 a year, it was clear that this sum was quite inadequate.

The society did not confine itself to beach activities. Many lecturers and demonstrators had been and would in the future be sent to country districts to try to teach as many people as possible methods of rescue, release and resuscitation, but unfortunately in the past the society had been very hampered in its work, as in 1929 the Government discontinued its grant of £200, and until 1937 it received no Government assistance. Last year the Government had made available the sum of £100, but the society considered this sum inadequate and was hopeful that the grant ere long would be increased.

The society depended on the generosity of the public for its finance, and it had great difficulty in this regard, as most people, when approached for donations, said that they contributed to the various hospitals and that they considered the society's work was of such national importance that the Government should subsidize it by a much larger amount.

The society was particularly pleased at being given the privilege of giving a demonstration before members of the British Medical Association, and it was sincerely hoped that as a result of the demonstration and the lectures given the doctors in the various municipalities would cooperate more fully with life-savers. Any doctor who cared to go along to any of the life-saving clubs and make himself known would be made very welcome, and after he had seen the keenness of the members in their work he would realize that the society deserved all the patronage and assistance it was possible to receive.

At this stage a party of four male and three female life-savers under an instructor gave a demonstration of rescue drill and release drill, and of the Silvester, Schäfer, Höljer-Neilson, and combination of Schäfer and Höljer-Neilson methods of resuscitation.

SIR JAMES BARRETT, at the invitation of the President, said that as he had been an early president of the Royal Life Saving Society of Victoria and was a permanent vice-president, he had seen a good deal of the work of the life-savers, and it was exceedingly good work. He recalled an incident at Phillip Island of attempted resuscitation after immersion in the water for five or six minutes; artificial respiration was continued for two and a half hours, and at that stage he had had to cut a blood vessel across at the wrist to show the life-savers that the circulation had stopped. On another occasion, at Barwon Heads, a boat had capsized and a Salvation Army lass had been rescued with difficulty after popping in and out of the waves for a long time; her body was water-logged and blue, and she was not breathing; they ran a lot of water out of her and managed to resuscitate her. In this case her head had not been completely under water for very long at any one time. Sir James Barrett commented that a young seal less than two months of age would drown in water and that even an old seal had to come up for air every four minutes. In conclusion he thanked Mr. Pleydell for his interesting address, and the life-savers for their valuable demonstration. He exhorted them to go on with artificial respiration until they were absolutely sure that recovery was impossible, and he congratulated them on the thorough, efficient and enthusiastic manner in which they did their work.

In reply to a question from Dr. Merrillees, Dr. Mollison stated that he could not remember any case in which a heavy meal had been the cause of death by drowning.

DR. W. W. OSTERMEYER expressed his appreciation of the work of the life-savers with which he was very familiar. He had noted the absence for some years past of Schäfer charts from the walls of public baths, and asked Mr. Pleydell whether it was because of lack of funds that they had not been replaced.

Mr. Pleydell replied that his society had supplied charts on frequent occasions, and only two years earlier they had printed more than five thousand charts, three thousand of which had been distributed in the past twelve months for baths and factories and to private householders.

DR. E. R. CORDNER said that he had been taught swimming and all types of resuscitation and release at Hegarty's Baths at the end of the previous century. The Silvester method was in use at that time, and he had then come across the man who held the record for staying under the surface for five minutes. This man had explained to Dr. Cordner how he did it by a trick; he sank and weighted an inverted tub on the day before the display and used the tub to get a breath of air while under water. Dr. Cordner had been very interested some eight or ten years later to hear that the record-holder had died while doing the trick; the body was found with the head under the tub, but the tub had been placed in a position in which the air had been replaced by escaping methane gas.

PROFESSOR MARSHALL ALLAN thanked Mr. Pleydell and the life-savers for coming to the meeting and for contributing to what had proved to be a valuable discussion, out of which he hoped a clearer understanding of points of view would lead to close and trusting cooperation between life-savers and the medical men and women in the saving of life on the beaches.

Correspondence.

ARTHUR YOUL NANKIVELL.

SIR: I regret that no obituary notice has appeared in the journal regarding the late Dr. Arthur Youl NanKivell, of Kerang. May I ask you to grant me a little space in an endeavour to make some amends to a very dear friend?

His death was typical of the man. Right up to within an hour of the end he carried out the onerous duties of a big general practice, and it was only afterwards that his local medical colleagues learned that he had been in very indifferent health during the few preceding days.

Disregard of personal feelings was a feature of NanKivell's work. His ability was so highly regarded in Kerang that he had built up a large consultant practice in the surrounding district. This often involved travel over roads which were almost impassable. But he was never known to refuse a call, though at times it meant horseback, walking miles through mud or pushing himself along on a trolly tram line. It did not matter; NanKivell got there just the same. The call of need was an irresistible appeal to his intensely human nature; and he never spared himself when he could relieve distress. The *Kerang Times* well summed up the situation when it stated that Dr. NanKivell burned himself out for others, and that he placed himself last when another needed his aid.

A colleague expresses himself as follows: "The home at Kerang of my dear old friend Dr. Arthur Youl NanKivell and his wife was one where their friends were welcomed

at any hour of the day or night, and where open-hearted hospitality of the most generous kind imaginable prevailed. The same kindly spirit was extended to all of Dr. NanKivell's patients, rich and poor; and this, combined with a very high standard of professional work, made him the trusted friend of one and all. His surgical skill was known, and he successfully undertook a wide range of surgical work in the excellently appointed local hospital.

His love of field sports went with a sound knowledge of the life history and habits of birds, beasts and fishes. At Kerang, one of the famous duck and quail shooting districts of Victoria, he delighted to organize parties that will never be forgotten by the visiting shooters; his greatest pleasure was to see them enjoy the sport. The dinner parties in his home after the day's shooting were one of the delights of the trip.

Arthur NanKivell was intensely interested in his family life; devoted to the welfare of his patients; a true sportsman and naturalist; a generous, kind and lovable companion."

NanKivell had a natural gift for surgery, and he had a large surgical practice in Kerang. He had great manual dexterity and, with his wide experience, his quick decision in doubtful and puzzling cases was a great consolation and help to the younger practitioners in the district, by whom his services as a consultant were in constant demand. His death is a loss which is being keenly felt by them at present.

Another feature of his life was his unbounded enthusiasm for anything he took up. He was associated as an official with practically every club and society in Kerang district. For many years he was a keen student of native fauna and was regarded as an authority on bird and reptile life. The Sportsmen's Association came into being solely through his efforts, his aim in this case being the preservation of native game. He was an enthusiastic collector of Australian aboriginal relics. In this sphere his reputation as an authority on the subject placed him in a favourable position, as people from far and near used to bring him specimens they thought might be interesting. The Museum of Anatomy at Canberra benefited as a result, as NanKivell presented everything of value to it. His photograph hangs in the museum in recognition of his gifts.

NanKivell's was a remarkable personality. He seemed to immediately gain the respect and confidence of all who came in contact with him, and as a citizen he had a high sense of the duties required of him. He was a most versatile man; though he had a busy general practice, he found time to read widely and interested himself enthusiastically in a myriad things outside his profession.

He was a most loyal, devoted and sincere friend with a rigid code of honesty and professional conduct. He was quite incapable of even a mean thought, and he died esteemed and respected by everyone. Right throughout the district news of his death brought a feeling of personal loss.

Yours, etc.,

DONALD G. MAY.

Barham,
New South Wales,
December 7, 1937.

GROUP HOSPITALIZATION.

SIR: In the *New York Times* of October 31 it is stated that at a cost varying from 2s. to £3 6s. a month more than 1,200,000 employees of firms and members of families have made it possible for themselves to receive the best of hospital care when they need it.

As previously stated, the system is identical in principle with the system in vogue at the Korumburra Bush Nursing Hospital.

By 1942 it is anticipated there will be 200 group hospitalization plans and 10,000,000 subscribers. The relationship of medical attendant to patient remains as in the Bush Nursing system—an individual and personal one.

Health insurance as we know it finds few if any medical supporters. The movement is characteristic of American individualism and dislike of government control.

Yours, etc.,

JAMES W. BARRETT.

103-105, Collins Street,
Melbourne, C.1,
December 8, 1937.

TUBERCULOSIS.

SIR: In the journal of the 11th instant Dr. Cotter Harvey mentions the mass fluoroscopy of chests abroad.

These series have been made mainly by enthusiastic physicians, and the radiologists have always stressed the point that the examinations were inadequate.

Cheapness has been the only excuse for making these examinations, and cheapness should not be considered when scientific accuracy is concerned. Another very bad thing about fluoroscopy is that the individual is told there is no trouble and is lulled into a false sense of security, and when examined properly at a later stage is found to have an extensive lesion. Of course, gross conditions like pneumothorax can be observed quite readily by screening, but not so that all-important early apical lesion.

As Dr. Cotter Harvey states, visual accommodation is a very important question, and no examination should ever be made unless the observer has been in total darkness for at least fifteen minutes by the clock.

The danger to the patient is certainly not very great, but the protection of the radiologist is still far from adequate and unnecessary exposure has to be avoided.

Yours, etc.,

J. G. EDWARDS.

185, Macquarie Street,
Sydney,
December 14, 1937.

SIR: The controversy about the relative merits of fluoroscopy and plate-taking in chest examination may have considerable influence on the policy to be followed in future surveys of the population, and as such merits full consideration.

I would appreciate, therefore, the opportunity of amplifying some remarks made at the recent meeting of the British Medical Association held in Adelaide last August.

There is no gainsaying the vital importance of X ray examination as an integral part of the investigation of any chest disease, declared or suspect, and it has been suggested that neglect to carry out this examination in such circumstances may be held to be as culpable as would be the failure to use radiography in a case of suspected fracture. (G. Jessel, *The Lancet*, November 6, 1937.) So the debate resolves itself into a discussion of the relative values of fluoroscopy and plate-taking, which are, of course, both essential for complete X ray examination.

The information obtained from fluoroscopy indicates the extent of movements of the component parts of the thoracic cage and the diaphragm, and the position of the mediastinum. The observer is able to compare and contrast the relative degrees of "lighting up" of lung zones, as well as notice the heart movements. Abnormal shadows may be localized, cavities (if large) seen, and fluid levels, either pleural or pulmonary, studied.

So is obtained a "living" picture of the state of the chest and its contents; but the knowledge is "personal", like the results of an ordinary clinical examination, and any report the observer may make will convey inadequately his interpretation of the examination.

Film-taking enables one to study in detail and at leisure any part of the lung field, and the various positions and techniques enable a full exploration to be made. It is as if one stayed the action of a motion picture to study one particular phase or detail.

Briefly, fluoroscopy gives a dynamic impression; plate-taking provides the corresponding "static" picture at a particular point.

Despite the remarks of Dr. Cotter Harvey (THE MEDICAL JOURNAL OF AUSTRALIA, December 11, 1937), and in agreement with Dr. J. G. Edwards, I consider that the finer details of the abnormal may easily be missed in a screen examination, and in a group survey for pulmonary tuberculosis the early cases may escape the notice of even the best dark-adapted eye.

Plate-taking, ensuring as it does the furnishing of a permanent record, allows of both consultation and review, eliminates errors inherent in the method of fluoroscopy, and permits the correct appreciation of later changes in the "follow-up".

Fluoroscopy has a very useful place in the periodic review of the "chronic" chest case, in the control of cases of artificial pneumothorax, and in the observation of the results of surgical procedures generally.

The extent and nature of any pathological change in the lungs can be appreciated best by the careful examination of an X ray film. All cases coming up for examination for the first time should have a film taken as a routine.

The omission of this technique, which provides the most precise and certain means available, may seriously invalidate the efficacy of any group survey in its most important function, that is, the detection of the early symptomless case of pulmonary tuberculosis.

Yours, etc.,

DAVID B. ROSENTHAL.

Gresswell Sanatorium,
Mont Park,
Victoria.
December 14, 1937.

UNUNITED FRACTURES.

SIR: I am very grateful to Dr. McClements Callow for his interest in my letter on the grafting of ununited fractures.

Perhaps I should have used the word "sometimes" instead of "often" in referring to the failure of grafts. I have had such a failure myself and know of four other surgeons who have had similar failures. In each case the graft was an inlay taken from the tibia. In each case great care was taken with technique, and in each case failure was due to lack of callus formation. Such a small number of cases mean nothing, of course, if bulk statistics are being worked out, but they mean a very great deal to individual surgeons. It must be remembered that the failure of a bone graft is a failure of the first magnitude. Everyone knows the long and weary road that leads to the grafting in the first place, and the longer and wearier road that leads from failure. Any surgeon who has had one failure is very anxious that he should not have another.

Dr. Callow obviously knows a great deal more about the histology of bone grafts than I do. Authorities seem to differ widely, however, on the fate of the graft. I have just received "Recent Advances in Orthopædic Surgery", by Burns and Ellis. The authors, in discussing the question of whether the graft lives or dies, say: "The truth probably lies between the two extremes. It is probable that transplants of small fragments with their periosteum may live, while in transplants of larger pieces of bone it is likely that the cells in the interior of the transplants eventually die, but that those near the surface continue to live and function." If, then, it is true that cells near the surface may live and function, would it not be better that such cells be full blown bone-formers than that they should be the inert cells one would expect in a recently cut graft.

I was very interested in reading further in the same chapter to find that Brooks has made the suggestion "that in old patients, when a bone grafting operation is contemplated, the periosteum in the region of the graft might be stimulated to proliferate by making saw cuts in the cortex of the bone about a week before transplantation". This is, in principle, the same suggestion as I have made.

What Dr. Callow says about not interfering with the fracture site when the granulating tissue masses from the opposing fragments are fusing is very sound, but I think that a technique could be devised which would reduce this to a minimum.

Again, Dr. Callow points out that delayed union of fractures of the neck of the femur is due to the poor supply to the capital fragment. It must be remembered, however, that although this blood supply may be too poor to allow the formation of granulation tissue, it is not too poor to keep the head of the femur alive. Who knows what stimulating effect the introduction of a large number of active bone-forming cells between the fragments might not have?

One's interest in these matters is aroused and maintained by discussion of this sort, but after all there is only one real method of testing out a suggestion. As Hunter said: "Don't think, try." I am afraid I will not have any opportunity of doing experimental work on the matter, but I sincerely hope someone else will.

Yours, etc.,

C. CRAIG.

Sotherton,
Brisbane Street,
Launceston,
Tasmania.
December 14, 1937.

Honours.

NEW YEAR HONOURS.

His Majesty the King has been pleased to confer the following honours on medical practitioners.

Dr. Earle Page, Minister for Commerce and Minister for Health of the Commonwealth, has been made a Knight Grand Cross of the Most Distinguished Order of Saint Michael and Saint George.

Dr. Norman Paul, of Sydney, has been created a Knight Bachelor.

Dr. John Newman Morris, of Melbourne, has been created a Companion of the Most Distinguished Order of Saint Michael and Saint George.

Dr. John Charles Fulton, of Launceston, has been created an Officer of the Most Excellent Order of the British Empire.

The congratulations of the medical profession are extended to Sir Earle Page, Sir Norman Paul, Dr. J. Newman Morris and Dr. J. C. Fulton.

Obituary.

LESLIE WYLIE NORMAN GIBSON.

WE regret to announce the death of Dr. Leslie Wylie Norman Gibson, which occurred on December 23, 1937, at Brisbane, Queensland.

JAMES HUNTER.

WE regret to announce the death of Dr. James Hunter, which occurred on December 24, 1937, at Sydney, New South Wales.

HERBERT HENRY BULLMORE.

WE regret to announce the death of Dr. Herbert Henry Bullmore, which occurred on December 28, 1937, at Sydney, New South Wales.

Books Received.

PULMONARY TUBERCULOSIS IN PRACTICE: A MODERN CONCEPTION, by R. C. Wingfield, B.A., M.B., B.Ch., F.R.C.P.; 1937. London: Edward Arnold and Company. Demy 8vo, pp. 127, with illustrations. Price: 9s. net.

MEDICAL RESEARCH COUNCIL OF THE PRIVY COUNCIL. SPECIAL REPORT SERIES, No. 225: INVESTIGATIONS INTO THE NATURE AND CHARACTERISTIC FEATURES OF POST-NORMAL OCCLUSION, by M. Young, E. Johnson, C. Smyth and M. Still; 1937. London: His Majesty's Stationery Office. Medium 8vo, pp. 106. Price: 1s. 6d. net.

RECENT ADVANCES IN ENTOMOLOGY, by A. D. Imms, M.A., D.Sc., F.R.S.; Second Edition; 1937. London: J. and A. Churchill Limited. Large crown 8vo, pp. 441, with illustrations. Price: 15s. net.

MEDICAL RESEARCH COUNCIL OF THE PRIVY COUNCIL. SPECIAL REPORT SERIES, No. 226: MEDICAL USES OF RADIUM. SUMMARY OF REPORTS FROM RESEARCH CENTRES FOR 1936; 1937. London: His Majesty's Stationery Office. Medium 8vo, pp. 55. Price: 1s. net.

DR. ALEXANDER THOMSON: A PIONEER OF MELBOURNE AND FOUNDER OF GEELONG, by R. H. Croll, in collaboration with R. R. Wettenhall; 1937. Melbourne: Robertson and Mullens. Crown 4to, pp. 61, with illustrations. Price: 7s. 6d. net.

LIFE AND DEATH: THE AUTOBIOGRAPHY OF A SURGEON, by A. Majocchi, translated by H. J. Stenning; 1937. London: George Allen and Unwin Limited. Demy 8vo, pp. 343. Price: 10s. 6d. net.

DISEASES OF THE NERVOUS SYSTEM IN INFANCY, CHILDHOOD AND ADOLESCENCE, by F. R. Ford, M.D.; 1937. London: Baillière, Tindall and Cox. Royal 8vo, pp. 977, with illustrations. Price: 38s. net.

ELECTROCARDIOGRAPHY, by C. C. Maher, B.S., M.D.; Second Edition; 1937. London: Baillière, Tindall and Cox. Super royal 8vo, pp. 270, with illustrations. Price: 18s. net.

A BRIEF OUTLINE OF MODERN TREATMENT OF FRACTURES, by H. W. Spiers, A.B., M.D.; Second Edition; 1937. London: Baillière, Tindall and Cox. Medium 8vo, pp. 146, with illustrations. Price: 9s. net.

Diary for the Month.

JAN. 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
JAN. 14.—Queensland Branch, B.M.A.: Council.
JAN. 26.—Victorian Branch, B.M.A.: Council.
JAN. 28.—Queensland Branch, B.M.A.: Council.
FEB. 1.—New South Wales Branch, B.M.A.: Organization and Science Committee.
FEB. 2.—Western Australian Branch, B.M.A.: Council.
FEB. 2.—Victorian Branch, B.M.A.: Branch.
FEB. 3.—South Australian Branch, B.M.A.: Council.
FEB. 4.—South Australian Branch, B.M.A.: Branch.
FEB. 8.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

Medical Appointments Vacant, etc.

For announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser," pages xviii to xx.

ALFRED HOSPITAL, MELBOURNE, VICTORIA: Medical Superintendent.
AUSTIN HOSPITAL FOR CANCER AND CHRONIC DISEASES, HEIDELBERG, VICTORIA: Honorary Assistant Surgeons.
DEPARTMENT OF PUBLIC HEALTH, PERTH, WESTERN AUSTRALIA: Medical Officer.
HOSPITALS COMMISSION, SYDNEY, NEW SOUTH WALES: Resident Medical Officers.
THE EASTERN SUBURBS HOSPITAL, SYDNEY, NEW SOUTH WALES: Temporary Relieving Honorary Assistant Physician.
THE UNIVERSITY OF MELBOURNE, VICTORIA: Staff Vacancies.
TOOWOOMBA HOSPITALS BOARD, TOOWOOMBA, QUEENSLAND: Resident Medical Officer.
WESTERN AUSTRALIAN PUBLIC SERVICE: Junior Medical Officer.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment referred to in the following table without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCHES.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135 Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries Australian Prudential Association, Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17	Brisbane Associate Friendly Societies' Medical Institute. Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.
SOUTH AUSTRALIAN: Secretary, 178 North Terrace, Adelaide.	All Lodge appointments in South Australia. All contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 205, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.

Editorial Notices.

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